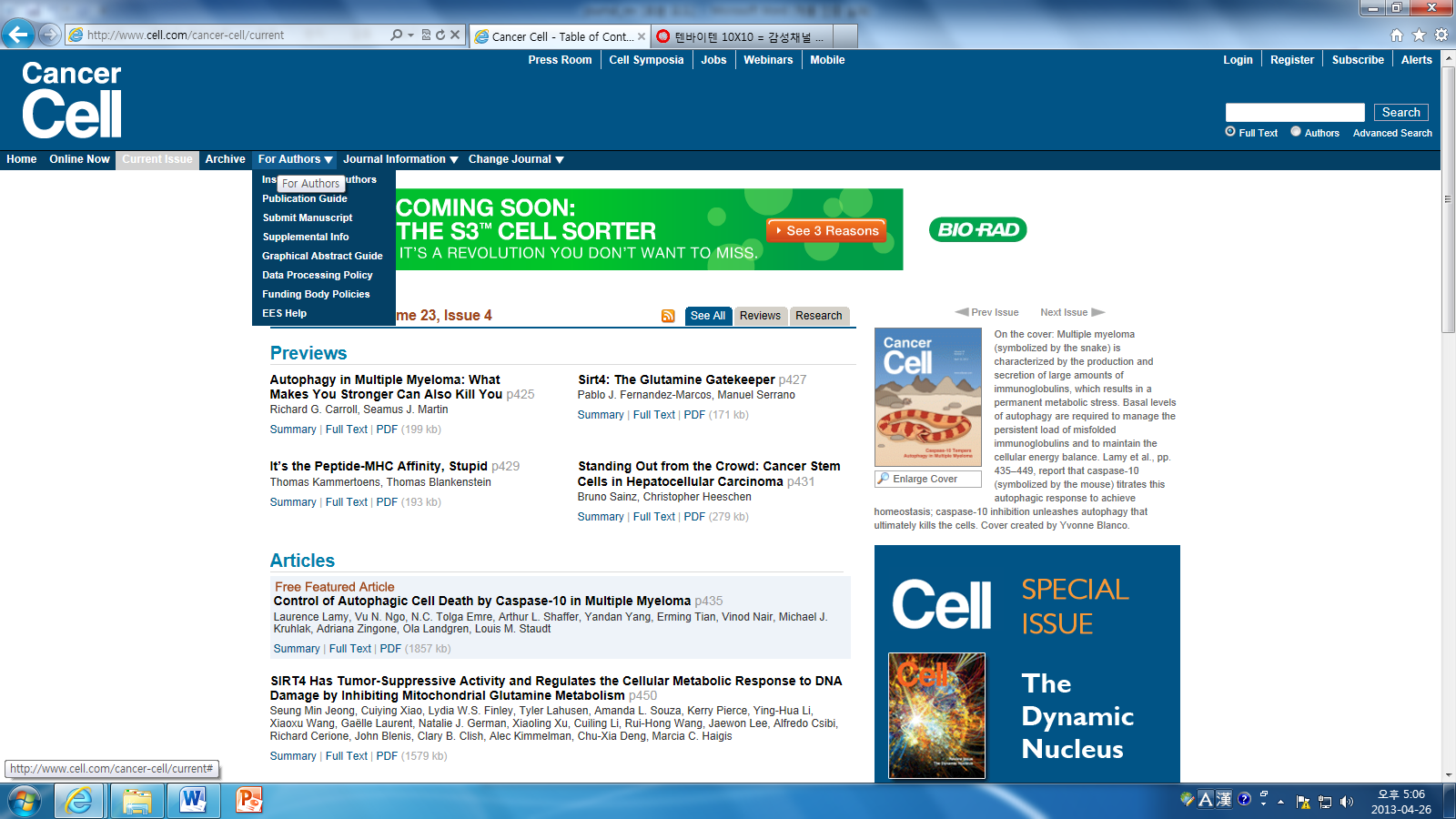
**MS**



**Preview**

**Autophagy in Multiple Myeloma: What Makes You Stronger Can Also Kill You**

[**Richard G. Carroll**](javascript:void(0);)**,** [**Seamus J. Martin**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00135-9)

Autophagy, a process for recycling cellular constituents, is normally associated with cell survival and is thought to be beneficial for tumor maintenance. However, in this issue of *Cancer Cell*, Lamy and colleagues report that multiple myeloma utilizes caspase-10 to restrain autophagy and undergoes autophagic cell death upon its removal or inhibition.



**Article**

**Control of Autophagic Cell Death by Caspase-10 in Multiple Myeloma**

[**Laurence Lamy**](javascript:void(0);)**,** [**Vu N. Ngo**](javascript:void(0);)**,** [**N.C. Tolga Emre**](javascript:void(0);)**,** [**Arthur L. Shaffer**](javascript:void(0);)**,** [**Yandan Yang**](javascript:void(0);)**,** [**Erming Tian**](javascript:void(0);)**,** [**Vinod Nair**](javascript:void(0);)**,** [**Michael J. Kruhlak**](javascript:void(0);)**,** [**Adriana Zingone**](javascript:void(0);)**,** [**Ola Landgren**](javascript:void(0);)**,** [**Louis M. Staudt**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00073-1)

**Summary**

We performed a loss-of-function RNA interference screen to define therapeutic targets in multiple myeloma, a genetically diverse plasma cell malignancy. Unexpectedly, we discovered that all myeloma lines require caspase-10 for survival irrespective of their genetic abnormalities. The transcription factor IRF4 induces both caspase-10 and its associated protein cFLIPL in myeloma, generating a protease that does not induce apoptosis but rather blocks an autophagy-dependent cell death pathway. Caspase-10 inhibits autophagy by cleaving the BCL2-interacting protein BCLAF1, itself a strong inducer of autophagy that acts by displacing beclin-1 from BCL2. While myeloma cells require a basal level of autophagy for survival, caspase-10 tempers this response to avoid cell death. Drugs that disrupt this vital balance may have therapeutic potential in myeloma.

**Preview**

**Sirt4: The Glutamine Gatekeeper**

[**Pablo J. Fernandez-Marcos**](javascript:void(0);)**,** [**Manuel Serrano**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00137-2)

Little is known about how DNA damage and metabolism are interconnected. In this issue of *Cancer Cell*, Jeong and colleagues report that an important component of the DNA damage response is the SIRT4-mediated blockade of glutamine catabolism. Failure to shut down glutamine consumption results in unscheduled proliferation, genomic instability, and cancer.

**Article**

**SIRT4 Has Tumor-Suppressive Activity and Regulates the Cellular Metabolic Response to DNA Damage by Inhibiting Mitochondrial Glutamine Metabolism**

**Authors**

[**Seung Min Jeong**](javascript:void(0);)**,** [**Cuiying Xiao**](javascript:void(0);)**,** [**Lydia W.S. Finley**](javascript:void(0);)**,** [**Tyler Lahusen**](javascript:void(0);)**,** [**Amanda L. Souza**](javascript:void(0);)**,** [**Kerry Pierce**](javascript:void(0);)**,** [**Ying-Hua Li**](javascript:void(0);)**,** [**Xiaoxu Wang**](javascript:void(0);)**,** [**Gaëlle Laurent**](javascript:void(0);)**,** [**Natalie J. German**](javascript:void(0);)**,** [**Xiaoling Xu**](javascript:void(0);)**,** [**Cuiling Li**](javascript:void(0);)**,** [**Rui-Hong Wang**](javascript:void(0);)**,** [**Jaewon Lee**](javascript:void(0);)**,** [**Alfredo Csibi**](javascript:void(0);)**,** [**Richard Cerione**](javascript:void(0);)**,** [**John Blenis**](javascript:void(0);)**,** [**Clary B. Clish**](javascript:void(0);)**,** [**Alec Kimmelman**](javascript:void(0);)**,** [**Chu-Xia Deng**](javascript:void(0);)send email**,** [**Marcia C. Haigis**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00078-0)

**Summary**

DNA damage elicits a cellular signaling response that initiates cell cycle arrest and DNA repair. Here, we find that DNA damage triggers a critical block in glutamine metabolism, which is required for proper DNA damage responses. This block requires the mitochondrial SIRT4, which is induced by numerous genotoxic agents and represses the metabolism of glutamine into tricarboxylic acid cycle. SIRT4 loss leads to both increased glutamine-dependent proliferation and stress-induced genomic instability, resulting in tumorigenic phenotypes. Moreover, SIRT4 knockout mice spontaneously develop lung tumors. Our data uncover SIRT4 as an important component of the DNA damage response pathway that orchestrates a metabolic block in glutamine metabolism, cell cycle arrest, and tumor suppression.

**Article**

**Lysine-5 Acetylation Negatively Regulates Lactate Dehydrogenase A and Is Decreased in Pancreatic Cancer**

[**Di Zhao**](javascript:void(0);)**,** [**Shao-Wu Zou**](javascript:void(0);)**,** [**Ying Liu**](javascript:void(0);)**,** [**Xin Zhou**](javascript:void(0);)**,** [**Yan Mo**](javascript:void(0);)**,** [**Ping Wang**](javascript:void(0);)**,** [**Yan-Hui Xu**](javascript:void(0);)**,** [**Bo Dong**](javascript:void(0);)**,** [**Yue Xiong**](javascript:void(0);)send email**,** [**Qun-Ying Lei**](javascript:void(0);)send email**,** [**Kun-Liang Guan**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00068-8)

**Summary**

Tumor cells commonly have increased glucose uptake and lactate accumulation. Lactate is produced from pyruvate by lactate dehydrogenase A (LDH-A), which is frequently overexpressed in tumor cells and is important for cell growth. Elevated transcription by c-Myc or HIF1α may contribute to increased LDH-A in some cancer types. Here, we show that LDH-A is acetylated at lysine 5 (K5) and that this acetylation inhibits LDH-A activity. Furthermore, the K5-acetylated LDH-A is recognized by the HSC70 chaperone and delivered to lysosomes for degradation. Replacement of endogenous LDH-A with an acetylation mimetic mutant decreases cell proliferation and migration. Importantly, K5 acetylation of LDH-A is reduced in human pancreatic cancers. Our study reveals a mechanism of LDH-A upregulation in pancreatic cancers.

**Article**

**The Pivotal Role of IKKα in the Development of Spontaneous Lung Squamous Cell Carcinomas**

[**Zuoxiang Xiao**](javascript:void(0);)**,** [**Qun Jiang**](javascript:void(0);)**,** [**Jami Willette-Brown**](javascript:void(0);)**,** [**Sichuan Xi**](javascript:void(0);)**,** [**Feng Zhu**](javascript:void(0);)**,** [**Sandra Burkett**](javascript:void(0);)**,** [**Timothy Back**](javascript:void(0);)**,** [**Na-Young Song**](javascript:void(0);)**,** [**Mahesh Datla**](javascript:void(0);)**,** [**Zhonghe Sun**](javascript:void(0);)**,** [**Romina Goldszmid**](javascript:void(0);)**,** [**Fanching Lin**](javascript:void(0);)**,** [**Travis Cohoon**](javascript:void(0);)**,** [**Kristen Pike**](javascript:void(0);)**,** [**Xiaolin Wu**](javascript:void(0);)**,** [**David S. Schrump**](javascript:void(0);)**,** [**Kwok-Kin Wong**](javascript:void(0);)**,** [**Howard A. Young**](javascript:void(0);)**,** [**Giorgio Trinchieri**](javascript:void(0);)**,** [**Robert H. Wiltrout**](javascript:void(0);)send email**,** [**Yinling Hu**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/cancer-cell/abstract/S1535-6108(13)00125-6)

**Summary**

Here, we report that kinase-dead IKKα knockin mice develop spontaneous lung squamous cell carcinomas (SCCs) associated with IKKα downregulation and marked pulmonary inflammation. IKKα reduction upregulated the expression of p63, Trim29, and keratin 5 (K5), which serve as diagnostic markers for human lung SCCs. IKKαlowK5+p63hi cell expansion and SCC formation were accompanied by inflammation-associated deregulation of oncogenes, tumor suppressors, and stem cell regulators. Reintroducing transgenic K5.IKKα, depleting macrophages, and reconstituting irradiated mutant animals with wild-type bone marrow (BM) prevented SCC development, suggesting that BM-derived IKKα mutant macrophages promote the transition of IKKαlowK5+p63hi cells to tumor cells. This mouse model resembles human lung SCCs, sheds light on the mechanisms underlying lung malignancy development, and identifies targets for therapy of lung SCCs.

[Sci Rep.](http://www.ncbi.nlm.nih.gov/pubmed/23604351) 2013 Apr 22;3:1690. doi: 10.1038/srep01690.

# Analysis of SUMOylated proteins using SUMO-traps.

[Da Silva-Ferrada E](http://www.ncbi.nlm.nih.gov/pubmed?term=Da%20Silva-Ferrada%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Xolalpa W](http://www.ncbi.nlm.nih.gov/pubmed?term=Xolalpa%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Lang V](http://www.ncbi.nlm.nih.gov/pubmed?term=Lang%20V%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Aillet F](http://www.ncbi.nlm.nih.gov/pubmed?term=Aillet%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Martin-Ruiz I](http://www.ncbi.nlm.nih.gov/pubmed?term=Martin-Ruiz%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [de la Cruz-Herrera CF](http://www.ncbi.nlm.nih.gov/pubmed?term=de%20la%20Cruz-Herrera%20CF%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Lopitz-Otsoa F](http://www.ncbi.nlm.nih.gov/pubmed?term=Lopitz-Otsoa%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Carracedo A](http://www.ncbi.nlm.nih.gov/pubmed?term=Carracedo%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Goldenberg SJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Goldenberg%20SJ%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Rivas C](http://www.ncbi.nlm.nih.gov/pubmed?term=Rivas%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [England P](http://www.ncbi.nlm.nih.gov/pubmed?term=England%20P%5BAuthor%5D&cauthor=true&cauthor_uid=23604351), [Rodríguez MS](http://www.ncbi.nlm.nih.gov/pubmed?term=Rodr%C3%ADguez%20MS%5BAuthor%5D&cauthor=true&cauthor_uid=23604351).

### Source

1] Proteomics Unit, CIC bioGUNE, CIBERehd, Bd. 801A, Bizkaia Technology Park, Derio, 48160, Bizkaia, Spain [2] Ubiquitylation and Cancer Molecular Biology. Inbiomed, Po Mikeletegi 81, San Sebastián 20009, Gipuzkoa, Spain.

### Abstract

SUMO-modified proteins are recognized by SUMO interacting motifs (SIMs), thus triggering diverse cellular responses. Here SIMs were used to develop SUMO-traps to capture endogenous SUMOylated proteins. Our results show that these small peptides are transferable motifs that maintain their SUMO binding capacity when fused to the heterologous carrier protein GST. The tandem disposition of SIMs increases the binding capacity of SUMO-traps to specifically interact with polySUMO but not poly-Ubiquitin chains. We demonstrate that this SUMO capturing system purifies SUMOylated proteins such as IκBα, PTEN, PML or p53 in vitro and in vivo. These properties can be used to explore the many critical functions regulated by protein SUMOylation.

[Mol Cell.](http://www.ncbi.nlm.nih.gov/pubmed/23453810) 2013 Apr 11;50(1):43-55. doi: 10.1016/j.molcel.2013.01.037. Epub 2013 Feb 28.

# MEK1 Is Required for PTEN Membrane Recruitment, AKT Regulation, and the Maintenance of Peripheral Tolerance.

[Zmajkovicova K](http://www.ncbi.nlm.nih.gov/pubmed?term=Zmajkovicova%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23453810), [Jesenberger V](http://www.ncbi.nlm.nih.gov/pubmed?term=Jesenberger%20V%5BAuthor%5D&cauthor=true&cauthor_uid=23453810), [Catalanotti F](http://www.ncbi.nlm.nih.gov/pubmed?term=Catalanotti%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23453810), [Baumgartner C](http://www.ncbi.nlm.nih.gov/pubmed?term=Baumgartner%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23453810), [Reyes G](http://www.ncbi.nlm.nih.gov/pubmed?term=Reyes%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23453810), [Baccarini M](http://www.ncbi.nlm.nih.gov/pubmed?term=Baccarini%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23453810).

### Source

Department of Microbiology and Immunobiology, Max F. Perutz Laboratories, University of Vienna, Doktor-Bohr-Gasse 9, 1030 Vienna, Austria.

### Abstract

The Raf/MEK/ERK and PI3K/Akt pathways are prominent effectors of oncogenic Ras. These pathways negatively regulate each other, but the mechanism involved is incompletely understood. We now identify MEK1 as an essential regulator of lipid/protein phosphatase PTEN, through which it controls phosphatidylinositol-3-phosphate accumulation and AKT signaling. MEK1 ablation stabilizes AKT activation and, in vivo, causes a lupus-like autoimmune disease and myeloproliferation. Mechanistically, MEK1 is necessary for PTEN membrane recruitment as part of a ternary complex containing the multidomain adaptor MAGI1. Complex formation is independent of MEK1 kinase activity but requires phosphorylation of T292 on MEK1 by activated ERK. Thus, inhibiting the ERK pathway reduces PTEN membrane recruitment, increasing phosphatidylinositol-3-phosphate accumulation and AKT activation. Our data offer a conceptual framework for the observation that activation of the PI3K pathway frequently mediate resistance to MEK inhibitors and for the promising results obtained by combined MEK/PI3K inhibition in preclinical cancer models.

2013 Mar 1;123(3):1157-75. doi: 10.1172/JCI63672. Epub 2013 Feb 22.

# Sprouty2, PTEN, and PP2A interact to regulate prostate cancer progression.

[Patel R](http://www.ncbi.nlm.nih.gov/pubmed?term=Patel%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Gao M](http://www.ncbi.nlm.nih.gov/pubmed?term=Gao%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Ahmad I](http://www.ncbi.nlm.nih.gov/pubmed?term=Ahmad%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Fleming J](http://www.ncbi.nlm.nih.gov/pubmed?term=Fleming%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Singh LB](http://www.ncbi.nlm.nih.gov/pubmed?term=Singh%20LB%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Rai TS](http://www.ncbi.nlm.nih.gov/pubmed?term=Rai%20TS%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [McKie AB](http://www.ncbi.nlm.nih.gov/pubmed?term=McKie%20AB%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Seywright M](http://www.ncbi.nlm.nih.gov/pubmed?term=Seywright%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Barnetson RJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Barnetson%20RJ%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Edwards J](http://www.ncbi.nlm.nih.gov/pubmed?term=Edwards%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Sansom OJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Sansom%20OJ%5BAuthor%5D&cauthor=true&cauthor_uid=23434594), [Leung HY](http://www.ncbi.nlm.nih.gov/pubmed?term=Leung%20HY%5BAuthor%5D&cauthor=true&cauthor_uid=23434594).

### Source

The Beatson Institute for Cancer Research, Glasgow, United Kingdom.

### Abstract

Concurrent activation of RAS/ERK and PI3K/AKT pathways is implicated in prostate cancer progression. The negative regulators of these pathways, including sprouty2 (SPRY2), protein phosphatase 2A (PP2A), and phosphatase and tensin homolog (PTEN), are commonly inactivated in prostate cancer. The molecular basis of cooperation between these genetic alterations is unknown. Here, we show that SPRY2 deficiency alone triggers activation of AKT and ERK, but this is insufficient to drive tumorigenesis. In addition to AKT and ERK activation, SPRY2 loss also activates a PP2A-dependent tumor suppressor checkpoint. Mechanistically, the PP2A-mediated growth arrest depends on GSK3β and is ultimately mediated by nuclear PTEN. In murine prostate cancer models, Pten haploinsufficiency synergized with Spry2 deficiency to drive tumorigenesis, including metastasis. Together, these results show that loss of Pten cooperates with Spry2 deficiency by bypassing a novel tumor suppressor checkpoint. Furthermore, loss of SPRY2 expression correlates strongly with loss of PTEN and/or PP2A subunits in human prostate cancer. This underlines the cooperation between SPRY2 deficiency and PTEN or PP2A inactivation in promoting tumorigenesis. Overall, we propose SPRY2, PTEN, and PP2A status as an important determinant of prostate cancer progression. Characterization of this trio may facilitate patient stratification for targeted therapies and chemopreventive interventions.

[Cell Res.](http://www.ncbi.nlm.nih.gov/pubmed/23419514) 2013 Apr;23(4):552-64. doi: 10.1038/cr.2013.27. Epub 2013 Feb 19.

# RFP-mediated ubiquitination of PTEN modulates its effect on AKT activation.

[Lee JT](http://www.ncbi.nlm.nih.gov/pubmed?term=Lee%20JT%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Shan J](http://www.ncbi.nlm.nih.gov/pubmed?term=Shan%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Zhong J](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhong%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Li M](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Zhou B](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhou%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Zhou A](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhou%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Parsons R](http://www.ncbi.nlm.nih.gov/pubmed?term=Parsons%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23419514), [Gu W](http://www.ncbi.nlm.nih.gov/pubmed?term=Gu%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23419514).

### Source

Institute for Cancer Genetics, and Department of Pathology and Cell Biology, College of Physicians and Surgeons, Columbia University, 1130 St Nicholas Avenue, New York, NY 10032, USA.

### Abstract

The PTEN tumor suppressor is a lipid phosphatase that has a central role in regulating the phosphatidylinositol-3-kinase (PI3K) signal transduction cascade. Nevertheless, the mechanism by which the PTEN activity is regulated in cells needs further elucidation. Although previous studies have shown that ubiquitination of PTEN can modulate its stability and subcellular localization, the role of ubiquitination in the most critical aspect of PTEN function, its phosphatase activity, has not been fully addressed. Here, we identify a novel E3 ubiquitin ligase of PTEN, Ret finger protein (RFP), that is able to promote atypical polyubiquitinations of PTEN. These ubiquitinations do not lead to PTEN instability or relocalization, but rather significantly inhibit PTEN phosphatase activity and therefore modulate its ability to regulate the PI3K signal transduction cascade. Indeed, RFP overexpression relieves PTEN-mediated inhibitory effects on AKT activation; in contrast, RNAi-mediated knockdown of endogenous RFP enhances the ability of PTEN to suppress AKT activation. Moreover, RFP-mediated ubiquitination of PTEN inhibits PTEN-dependent activation of TRAIL expression and also suppresses its ability to induce apoptosis. Our findings demonstrate a crucial role of RFP-mediated ubiquitination in controlling PTEN activity.

[Mol Cell.](http://www.ncbi.nlm.nih.gov/pubmed/23453806) 2013 Mar 28;49(6):1167-75. doi: 10.1016/j.molcel.2013.01.035. Epub 2013 Feb 28.

# AMPK-Dependent Degradation of TXNIP upon Energy Stress Leads to Enhanced Glucose Uptake via GLUT1.

[Wu N](http://www.ncbi.nlm.nih.gov/pubmed?term=Wu%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Zheng B](http://www.ncbi.nlm.nih.gov/pubmed?term=Zheng%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Shaywitz A](http://www.ncbi.nlm.nih.gov/pubmed?term=Shaywitz%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Dagon Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Dagon%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Tower C](http://www.ncbi.nlm.nih.gov/pubmed?term=Tower%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Bellinger G](http://www.ncbi.nlm.nih.gov/pubmed?term=Bellinger%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Shen CH](http://www.ncbi.nlm.nih.gov/pubmed?term=Shen%20CH%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Wen J](http://www.ncbi.nlm.nih.gov/pubmed?term=Wen%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Asara J](http://www.ncbi.nlm.nih.gov/pubmed?term=Asara%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [McGraw TE](http://www.ncbi.nlm.nih.gov/pubmed?term=McGraw%20TE%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Kahn BB](http://www.ncbi.nlm.nih.gov/pubmed?term=Kahn%20BB%5BAuthor%5D&cauthor=true&cauthor_uid=23453806), [Cantley LC](http://www.ncbi.nlm.nih.gov/pubmed?term=Cantley%20LC%5BAuthor%5D&cauthor=true&cauthor_uid=23453806).

### Source

Department of Systems Biology, Harvard Medical School, Boston, MA 02115, USA; Division of Signal Transduction, Beth Israel Deaconess Medical Center, Boston, MA 02115, USA.

### Abstract

Thioredoxin-interacting protein (TXNIP) is an α-arrestin family protein that is induced in response to glucose elevation. It has been shown to provide a negative feedback loop to regulate glucose uptake into cells, though the biochemical mechanism of action has been obscure. Here, we report that TXNIP suppresses glucose uptake directly, by binding to the glucose transporter GLUT1 and inducing GLUT1 internalization through clathrin-coated pits, as well as indirectly, by reducing the level of GLUT1 messenger RNA (mRNA). In addition, we show that energy stress results in the phosphorylation of TXNIP by AMP-dependent protein kinase (AMPK), leading to its rapid degradation. This suppression of TXNIP results in an acute increase in GLUT1 function and an increase in GLUT1 mRNA (hence the total protein levels) for long-term adaptation. The glucose influx through GLUT1 restores ATP-to-ADP ratios in the short run and ultimately induces TXNIP protein production to suppress glucose uptake once energy homeostasis is reestablished.

**KJ**

J Am Heart Assoc. 2013 Apr 22

[Cardiac and Renal Protective Effects of Irbesartan via **Peroxisome** **Proliferator-Activated** Receptorγ-Hepatocyte Growth Factor Pathway Independent of Angiotensin II Type 1a Receptor Blockade in Mouse Model of Salt-Sensitive Hypertension.](http://www.ncbi.nlm.nih.gov/pubmed/23608606)

Kusunoki H, Taniyama Y, Rakugi H, Morishita R.

Scand J Clin Lab Invest. 2013 Apr 23.

[**Peroxisome** **proliferator activated** receptor (**PPAR**)-gamma concentrations in childhood obesity.](http://www.ncbi.nlm.nih.gov/pubmed/23607613)

Akyürek N, Aycan Z, Cetinkaya S, Akyürek O, Yilmaz Ağladioğlu S, Ertan U.

J Lipid Res. 2013 Apr 20.

[Fatty acids regulate perilipin5 in muscle by activating **PPAR**δ](http://www.ncbi.nlm.nih.gov/pubmed/23606724)

Bindesboell C, Berg O, Arntsen B, Nebb HI, Dalen KT.

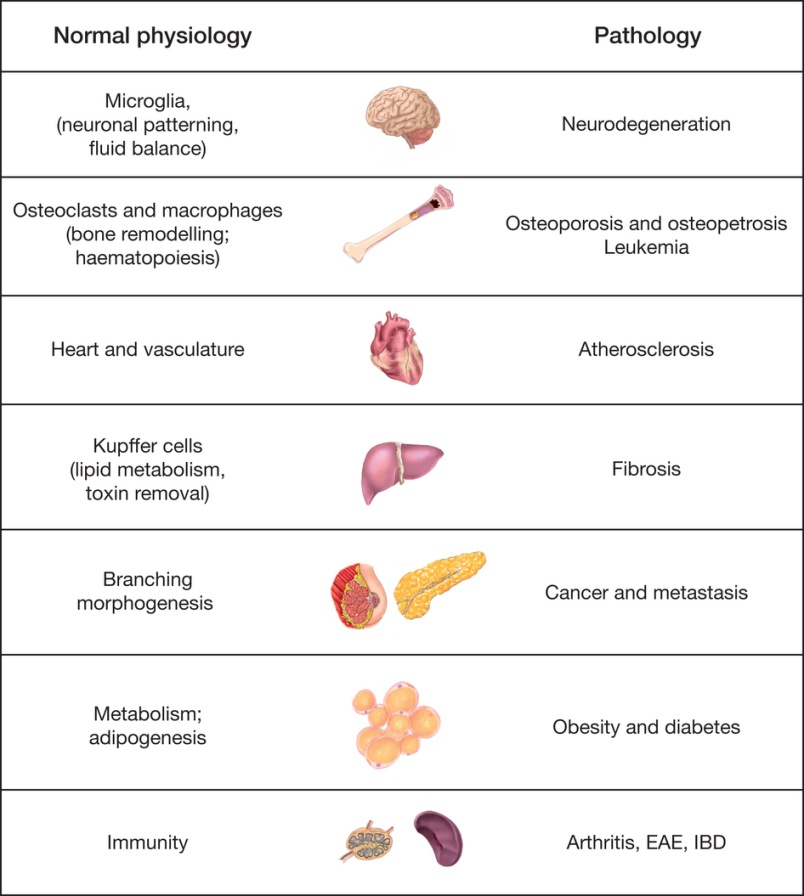
***Nature***

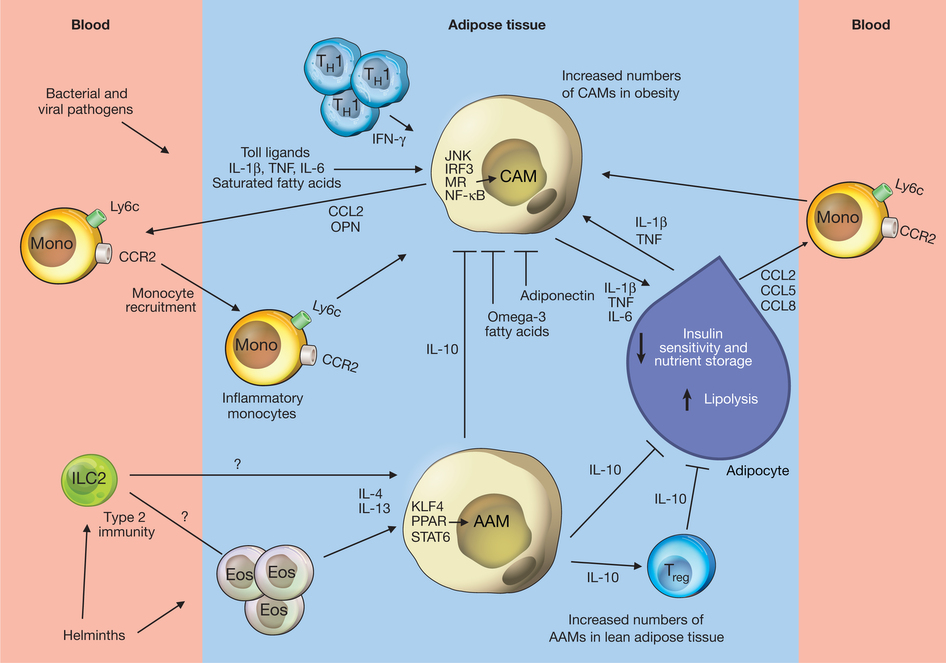
# Review

[**Top**](http://www.nature.com/nature/current_issue.html#top)

* [**Macrophage biology in development, homeostasis and disease**](http://www.nature.com/nature/journal/v496/n7446/full/nature12034.html)
  + Thomas A. Wynn,
  + Ajay Chawla &
  + Jeffrey W. Pollard

A discussion of progress in macrophage biology, examining their classification, diverse lineages, identities and regulation, their roles in regulating normal physiology and development, and their identification as therapeutic targets in human diseases.





# Articles

[**Top**](http://www.nature.com/nature/current_issue.html#top)

* [**Classical command of quantum systems**](http://www.nature.com/nature/journal/v496/n7446/full/nature12035.html)
  + Ben W. Reichardt,
  + Falk Unger &
  + Umesh Vazirani

A scheme is described that enables characterization and classical command of large quantum systems; it provides a test of whether a claimed quantum computer is truly quantum, and also advances towards a goal of quantum cryptography, namely the use of untrusted devices to establish a shared random key, with security based on the validity of quantum physics.

**See also**

* + [News & Views by Pironio & Aharonov](http://www.nature.com/nature/journal/v496/n7446/full/496436a.html)
* [**Dynamic regulatory network controlling TH17 cell differentiation**](http://www.nature.com/nature/journal/v496/n7446/full/nature11981.html)
  + Nir Yosef,
  + Alex K. Shalek,
  + Jellert T. Gaublomme,
  + Hulin Jin,
  + Youjin Lee,
  + Amit Awasthi,
  + Chuan Wu,
  + Katarzyna Karwacz,
  + Sheng Xiao,
  + Marsela Jorgolli,
  + David Gennert,
  + Rahul Satija,
  + Arvind Shakya,
  + Diana Y. Lu,
  + John J. Trombetta,
  + Meenu R. Pillai,
  + Peter J. Ratcliffe,
  + Mathew L. Coleman,
  + Mark Bix,
  + Dean Tantin,
  + Hongkun Park,
  + Vijay K. Kuchroo &
  + Aviv Regev
  + [+ et al.](javascript:;)

A global view of the genetic networks regulating the differentiation of TH17 cells is presented, based on temporal expression profiling, computational network reconstruction and validation of predicted interactions by nanowire-mediated siRNA perturbation.

* [**Co-evolution of a broadly neutralizing HIV-1 antibody and founder virus**](http://www.nature.com/nature/journal/v496/n7446/full/nature12053.html)
  + Hua-Xin Liao,
  + Rebecca Lynch,
  + Tongqing Zhou,
  + Feng Gao,
  + S. Munir Alam,
  + Scott D. Boyd,
  + Andrew Z. Fire,
  + Krishna M. Roskin,
  + Chaim A. Schramm,
  + Zhenhai Zhang,
  + Jiang Zhu,
  + Lawrence Shapiro,
  + NISC Comparative Sequencing Program,
  + James C. Mullikin,
  + S. Gnanakaran,
  + Peter Hraber,
  + Kevin Wiehe,
  + Garnett Kelsoe,
  + Guang Yang,
  + Shi-Mao Xia,
  + David C. Montefiori,
  + Robert Parks,
  + Krissey E. Lloyd,
  + Richard M. Scearce,
  + Kelly A. Soderberg,
  + Myron Cohen,
  + Gift Kamanga,
  + Mark K. Louder,
  + Lillian M. Tran,
  + Yue Chen,
  + Fangping Cai,
  + Sheri Chen,
  + Stephanie Moquin,
  + Xiulian Du,
  + M. Gordon Joyce,
  + Sanjay Srivatsan,
  + Baoshan Zhang,
  + Anqi Zheng,
  + George M. Shaw,
  + Beatrice H. Hahn,
  + Thomas B. Kepler,
  + Bette T. M. Korber,
  + Peter D. Kwong,
  + John R. Mascola &
  + Barton F. Haynes
  + [+ et al.](javascript:;)

Longitudinal sampling is used to map the evolution of an HIV-1 virus from the time of infection, and the co-evolution of a broadly neutralizing antibody in the same infected patient; the findings have important implications for HIV vaccine development.

**See also**

* + [News & Views by Mouquet & Nussenzweig](http://www.nature.com/nature/journal/v496/n7446/full/nature12091.html)
* [**Accurate assessment of mass, models and resolution by small-angle scattering**](http://www.nature.com/nature/journal/v496/n7446/full/nature12070.html)
  + Robert P. Rambo &
  + John A. Tainer

Small-angle scattering of X-rays or neutrons is more readily applied to macromolecular complexes than is X-ray crystallography, and is particularly useful for protein complexes with high flexibility; here new quantitative metrics are presented that will allow solution-derived structures to be validated and assessed for mass, resolution and accuracy.

# Letters

[**Top**](http://www.nature.com/nature/current_issue.html#top)

* [**Experimental realization of non-Abelian non-adiabatic geometric gates**](http://www.nature.com/nature/journal/v496/n7446/full/nature12010.html)
  + A. A. Abdumalikov Jr,
  + J. M. Fink,
  + K. Juliusson,
  + M. Pechal,
  + S. Berger,
  + A. Wallraff &
  + S. Filipp
  + [+ et al.](javascript:;)

Microwave stimulation of a superconducting artificial three-level atom is used to demonstrate high-fidelity, non-Abelian geometric transformations, the results of which depend on the order in which they are performed.

* [**Optical magnetic imaging of living cells**](http://www.nature.com/nature/journal/v496/n7446/full/nature12072.html)
  + D. Le Sage,
  + K. Arai,
  + D. R. Glenn,
  + S. J. DeVience,
  + L. M. Pham,
  + L. Rahn-Lee,
  + M. D. Lukin,
  + A. Yacoby,
  + A. Komeili &
  + R. L. Walsworth
  + [+ et al.](javascript:;)

A diamond chip with nitrogen–vacancy centres is used for magnetic imaging of living magnetotactic bacteria with sub-cellular spatial resolution.

**See also**

* + [News & Views by Pósfai & Dunin-Borkowski](http://www.nature.com/nature/journal/v496/n7446/full/496442a.html)
* [**Anomalous sulphur isotopes in plume lavas reveal deep mantle storage of Archaean crust**](http://www.nature.com/nature/journal/v496/n7446/full/nature12020.html)
  + Rita A. Cabral,
  + Matthew G. Jackson,
  + Estelle F. Rose-Koga,
  + Kenneth T. Koga,
  + Martin J. Whitehouse,
  + Michael A. Antonelli,
  + James Farquhar,
  + James M. D. Day &
  + Erik H. Hauri
  + [+ et al.](javascript:;)

Mass-independent fractionation of sulphur isotopes in basalts from the oceanic island of Mangaia (Cook Islands) indicates ancient subducted Archaean (>2.45 Gyr) oceanic crust and lithosphere survives in the mantle to be sampled beneath hotspot volcanoes.

* [**A systematic genome-wide analysis of zebrafish protein-coding gene function**](http://www.nature.com/nature/journal/v496/n7446/full/nature11992.html)
  + Ross N. W. Kettleborough,
  + Elisabeth M. Busch-Nentwich,
  + Steven A. Harvey,
  + Christopher M. Dooley,
  + Ewart de Bruijn,
  + Freek van Eeden,
  + Ian Sealy,
  + Richard J. White,
  + Colin Herd,
  + Isaac J. Nijman,
  + Fruzsina Fényes,
  + Selina Mehroke,
  + Catherine Scahill,
  + Richard Gibbons,
  + Neha Wali,
  + Samantha Carruthers,
  + Amanda Hall,
  + Jennifer Yen,
  + Edwin Cuppen &
  + Derek L. Stemple
  + [+ et al.](javascript:;)

A project to identify the phenotypes of disruptive mutations in every zebrafish protein-coding gene has so far revealed potentially disruptive mutations in more than 38% of the protein-coding genes, and the phenotypic consequences of each allele can be assessed using a novel multi-allelic phenotyping scheme.

**See also**

* + [News & Views by Schier](http://www.nature.com/nature/journal/v496/n7446/full/nature12094.html)
* [**The zebrafish reference genome sequence and its relationship to the human genome**](http://www.nature.com/nature/journal/v496/n7446/full/nature12111.html)**Open**
  + Kerstin Howe,
  + Matthew D. Clark,
  + Carlos F. Torroja,
  + James Torrance,
  + Camille Berthelot,
  + Matthieu Muffato,
  + John E. Collins,
  + Sean Humphray,
  + Karen McLaren,
  + Lucy Matthews,
  + Stuart McLaren,
  + Ian Sealy,
  + Mario Caccamo,
  + Carol Churcher,
  + Carol Scott,
  + Jeffrey C. Barrett,
  + Romke Koch,
  + Gerd-Jörg Rauch,
  + Simon White,
  + William Chow,
  + Britt Kilian,
  + Leonor T. Quintais,
  + José A. Guerra-Assunção,
  + Yi Zhou,
  + Yong Gu,
  + Jennifer Yen,
  + Jan-Hinnerk Vogel,
  + Tina Eyre,
  + Seth Redmond,
  + Ruby Banerjee,
  + Jianxiang Chi,
  + Beiyuan Fu,
  + Elizabeth Langley,
  + Sean F. Maguire,
  + Gavin K. Laird,
  + David Lloyd,
  + Emma Kenyon,
  + Sarah Donaldson,
  + Harminder Sehra,
  + Jeff Almeida-King,
  + Jane Loveland,
  + Stephen Trevanion,
  + Matt Jones,
  + Mike Quail,
  + Dave Willey,
  + Adrienne Hunt,
  + John Burton,
  + Sarah Sims,
  + Kirsten McLay,
  + Bob Plumb,
  + Joy Davis,
  + Chris Clee,
  + Karen Oliver,
  + Richard Clark,
  + Clare Riddle,
  + David Eliott,
  + Glen Threadgold,
  + Glenn Harden,
  + Darren Ware,
  + Beverly Mortimer,
  + Giselle Kerry,
  + Paul Heath,
  + Benjamin Phillimore,
  + Alan Tracey,
  + Nicole Corby,
  + Matthew Dunn,
  + Christopher Johnson,
  + Jonathan Wood,
  + Susan Clark,
  + Sarah Pelan,
  + Guy Griffiths,
  + Michelle Smith,
  + Rebecca Glithero,
  + Philip Howden,
  + Nicholas Barker,
  + Christopher Stevens,
  + Joanna Harley,
  + Karen Holt,
  + Georgios Panagiotidis,
  + Jamieson Lovell,
  + Helen Beasley,
  + Carl Henderson,
  + Daria Gordon,
  + Katherine Auger,
  + Deborah Wright,
  + Joanna Collins,
  + Claire Raisen,
  + Lauren Dyer,
  + Kenric Leung,
  + Lauren Robertson,
  + Kirsty Ambridge,
  + Daniel Leongamornlert,
  + Sarah McGuire,
  + Ruth Gilderthorp,
  + Coline Griffiths,
  + Deepa Manthravadi,
  + Sarah Nichol,
  + Gary Barker,
  + Siobhan Whitehead,
  + Michael Kay,
  + Jacqueline Brown,
  + Clare Murnane,
  + Emma Gray,
  + Matthew Humphries,
  + Neil Sycamore,
  + Darren Barker,
  + David Saunders,
  + Justene Wallis,
  + Anne Babbage,
  + Sian Hammond,
  + Maryam Mashreghi-Mohammadi,
  + Lucy Barr,
  + Sancha Martin,
  + Paul Wray,
  + Andrew Ellington,
  + Nicholas Matthews,
  + Matthew Ellwood,
  + Rebecca Woodmansey,
  + Graham Clark,
  + James Cooper,
  + Anthony Tromans,
  + Darren Grafham,
  + Carl Skuce,
  + Richard Pandian,
  + Robert Andrews,
  + Elliot Harrison,
  + Andrew Kimberley,
  + Jane Garnett,
  + Nigel Fosker,
  + Rebekah Hall,
  + Patrick Garner,
  + Daniel Kelly,
  + Christine Bird,
  + Sophie Palmer,
  + Ines Gehring,
  + Andrea Berger,
  + Christopher M. Dooley,
  + Zübeyde Ersan-Ürün,
  + Cigdem Eser,
  + Horst Geiger,
  + Maria Geisler,
  + Lena Karotki,
  + Anette Kirn,
  + Judith Konantz,
  + Martina Konantz,
  + Martina Oberländer,
  + Silke Rudolph-Geiger,
  + Mathias Teucke,
  + Kazutoyo Osoegawa,
  + Baoli Zhu,
  + Amanda Rapp,
  + Sara Widaa,
  + Cordelia Langford,
  + Fengtang Yang,
  + Nigel P. Carter,
  + Jennifer Harrow,
  + Zemin Ning,
  + Javier Herrero,
  + Steve M. J. Searle,
  + Anton Enright,
  + Robert Geisler,
  + Ronald H. A. Plasterk,
  + Charles Lee,
  + Monte Westerfield,
  + Pieter J. de Jong,
  + Leonard I. Zon,
  + John H. Postlethwait,
  + Christiane Nüsslein-Volhard,
  + Tim J. P. Hubbard,
  + Hugues Roest Crollius,
  + Jane Rogers &
  + Derek L. Stemple
  + [+ et al.](javascript:;)

A high-quality sequence assembly of the zebrafish genome reveals the largest gene set of any vertebrate and provides information on key genomic features, and comparison to the human reference genome shows that approximately 70% of human protein-coding genes have at least one clear zebrafish orthologue.

**See also**

* + [News & Views by Schier](http://www.nature.com/nature/journal/v496/n7446/full/nature12094.html)
* [**The global distribution and burden of dengue**](http://www.nature.com/nature/journal/v496/n7446/full/nature12060.html)
  + Samir Bhatt,
  + Peter W. Gething,
  + Oliver J. Brady,
  + Jane P. Messina,
  + Andrew W. Farlow,
  + Catherine L. Moyes,
  + John M. Drake,
  + John S. Brownstein,
  + Anne G. Hoen,
  + Osman Sankoh,
  + Monica F. Myers,
  + Dylan B. George,
  + Thomas Jaenisch,
  + G. R. William Wint,
  + Cameron P. Simmons,
  + Thomas W. Scott,
  + Jeremy J. Farrar &
  + Simon I. Hay
  + [+ et al.](javascript:;)

The public health burden of dengue is unknown; here cartographic approaches are used to provide insight into the global, regional and national burden of dengue, with the finding that the global number of infections per year is around 390 million, more than three times the estimate of the World Health Organization.

* [**Diverse type VI secretion phospholipases are functionally plastic antibacterial effectors**](http://www.nature.com/nature/journal/v496/n7446/full/nature12074.html)
  + Alistair B. Russell,
  + Michele LeRoux,
  + Krisztina Hathazi,
  + Danielle M. Agnello,
  + Takahiko Ishikawa,
  + Paul A. Wiggins,
  + Sun Nyunt Wai &
  + Joseph D. Mougous
  + [+ et al.](javascript:;)

A functionally diverse superfamily of bacterial phospholipase enzymes that mediate antagonisitc interactions as effectors of the type VI secretion system is uncovered; these enzymes degrade the bacterial membrane, representing a novel mechanism of bacterial competition.

* [**Induction of pathogenic TH17 cells by inducible salt-sensing kinase SGK1**](http://www.nature.com/nature/journal/v496/n7446/full/nature11984.html)
  + Chuan Wu,
  + Nir Yosef,
  + Theresa Thalhamer,
  + Chen Zhu,
  + Sheng Xiao,
  + Yasuhiro Kishi,
  + Aviv Regev &
  + Vijay K. Kuchroo
  + [+ et al.](javascript:;)

Transcriptional profiling of developing TH17 cells identifies serum glucocorticoid kinase 1 (SGK1) as an essential node downstream of IL-23 signalling, and transcriptional analysis shows that a modest increase in salt concentration induces SGK1 expression, promotes IL-23 receptor expression and enhances TH17 cell differentiation, accelerating the development of autoimmunity.

**See also**

* + [News & Views by O'Shea & Jones](http://www.nature.com/nature/journal/v496/n7446/full/nature11959.html)
* [**Sodium chloride drives autoimmune disease by the induction of pathogenic TH17 cells**](http://www.nature.com/nature/journal/v496/n7446/full/nature11868.html)
  + Markus Kleinewietfeld,
  + Arndt Manzel,
  + Jens Titze,
  + Heda Kvakan,
  + Nir Yosef,
  + Ralf A. Linker,
  + Dominik N. Muller &
  + David A. Hafler
  + [+ et al.](javascript:;)

Increased salt concentrations are shown to induce murine and human TH17 cells by a mechanism that depends on activation of p38/MAPK, NFAT5 and SGK1; mice kept on a high-salt diet develop a more severe experimental autoimmune encephalomyelitis due to increased induction of TH17 cells.

**See also**

* + [News & Views by O'Shea & Jones](http://www.nature.com/nature/journal/v496/n7446/full/nature11959.html)
* [**Follicular T-helper cell recruitment governed by bystander B cells and ICOS-driven motility**](http://www.nature.com/nature/journal/v496/n7446/full/nature12058.html)
  + Heping Xu,
  + Xuanying Li,
  + Dan Liu,
  + Jianfu Li,
  + Xu Zhang,
  + Xin Chen,
  + Shiyue Hou,
  + Lixia Peng,
  + Chenguang Xu,
  + Wanli Liu,
  + Lianfeng Zhang &
  + Hai Qi
  + [+ et al.](javascript:;)

ICOS ligand expression by bystander B cells is shown to induce pseudopod extension and migration of CXCR5-expressing T-helper cells into B-cell follicles, where they provide help to cognate B cells for germinal centre development.

* [**High-level semi-synthetic production of the potent antimalarial artemisinin**](http://www.nature.com/nature/journal/v496/n7446/full/nature12051.html)
  + C. J. Paddon,
  + P. J. Westfall,
  + D. J. Pitera,
  + K. Benjamin,
  + K. Fisher,
  + D. McPhee,
  + M. D. Leavell,
  + A. Tai,
  + A. Main,
  + D. Eng,
  + D. R. Polichuk,
  + K. H. Teoh,
  + D. W. Reed,
  + T. Treynor,
  + J. Lenihan,
  + H. Jiang,
  + M. Fleck,
  + S. Bajad,
  + G. Dang,
  + D. Dengrove,
  + D. Diola,
  + G. Dorin,
  + K. W. Ellens,
  + S. Fickes,
  + J. Galazzo,
  + S. P. Gaucher,
  + T. Geistlinger,
  + R. Henry,
  + M. Hepp,
  + T. Horning,
  + T. Iqbal,
  + L. Kizer,
  + B. Lieu,
  + D. Melis,
  + N. Moss,
  + R. Regentin,
  + S. Secrest,
  + H. Tsuruta,
  + R. Vazquez,
  + L. F. Westblade,
  + L. Xu,
  + M. Yu,
  + Y. Zhang,
  + L. Zhao,
  + J. Lievense,
  + P. S. Covello,
  + J. D. Keasling,
  + K. K. Reiling,
  + N. S. Renninger &
  + J. D. Newman
  + [+ et al.](javascript:;)

*Saccharomyces cerevisiae* is engineered to produce high concentrations of artemisinic acid, a precursor of the artemisinin used in combination therapies for malaria treatment; an efficient and practical chemical process to convert artemisinic acid to artemisinin is also developed.

* [**Crystal structure of a eukaryotic phosphate transporter**](http://www.nature.com/nature/journal/v496/n7446/full/nature12042.html)
  + Bjørn P. Pedersen,
  + Hemant Kumar,
  + Andrew B. Waight,
  + Aaron J. Risenmay,
  + Zygy Roe-Zurz,
  + Bryant H. Chau,
  + Avner Schlessinger,
  + Massimiliano Bonomi,
  + William Harries,
  + Andrej Sali,
  + Atul K. Johri &
  + Robert M. Stroud
  + [+ et al.](javascript:;)

The X-ray crystal structure of a high-affinity phosphate importer in an inward-facing, occluded state in the presence of phosphate is reported; this is the first structure of a membrane protein involved in inorganic phosphate uptake and the first crystal structure of a eukaryotic MFS transporter.

**HSY**

[J Biol Chem.](http://www.ncbi.nlm.nih.gov/pubmed/23589305) 2013 Apr 15. [Epub ahead of print]

**Heat shock protein 90 (Hsp90) selectively regulates the stability of KDM4B/JMJD2B histone demethylase.**

[Ipenberg I](http://www.ncbi.nlm.nih.gov/pubmed?term=Ipenberg%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23589305), [Guttmann-Raviv N](http://www.ncbi.nlm.nih.gov/pubmed?term=Guttmann-Raviv%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23589305), [Khoury HP](http://www.ncbi.nlm.nih.gov/pubmed?term=Khoury%20HP%5BAuthor%5D&cauthor=true&cauthor_uid=23589305), [Kupershmit I](http://www.ncbi.nlm.nih.gov/pubmed?term=Kupershmit%20I%5BAuthor%5D&cauthor=true&cauthor_uid=23589305), [Ayoub N](http://www.ncbi.nlm.nih.gov/pubmed?term=Ayoub%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23589305).

**Source**

Technion-Israel Institute of Technology, Israel.

**Abstract**

The family of KDM4A-D histone demethylases selectively demethylates H3K9 and H3K36, and is implicated in key cellular processes including DNA damage response, transcription, cell-cycle regulation, cellular differentiation, senescence and carcinogenesis. Various human cancers exhibit elevated protein levels of KDM4A-D members and their depletion impairs tumor formation, suggesting that their enhanced activity promotes carcinogenesis. However, the mechanisms regulating the KDM4 protein stability remain largely unknown. Here, we show that the molecular chaperon Hsp90 interacts and stabilizes KDM4B protein. Pharmacological inhibition of Hsp90 with geldanamycin (GA) resulted in ubiquitin-dependent proteasomal degradation of KDM4B, but not of KDM4C, suggesting that the turnover of these demethylases is regulated by distinct mechanisms. This degradation was accompanied by increased methylation of H3K9. We further show that KDM4B is ubiquitinated on lysines 337 and 562; simultaneous substitution of these residues to arginine suppressed the GA-induced degradation of KDM4B, suggesting that the ubiquitination of K337 and K562 targets KDM4B for proteasomal degradation upon Hsp90 inhibition. These findings constitute a novel pathway by which Hsp90 activity alters the histone code via regulation of KDM4B stability. This pathway may prove a druggable target for the treatment of tumors driven by enhanced KDM4B activity.

## **Rad51 replication fork recruitment is required for DNA damage tolerance**

Román González-Prieto[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201373a.html#a1), Ana M Muñoz-Cabello[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201373a.html#a1), María J Cabello-Lobato[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201373a.html#a1) and Félix Prado[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201373a.html#a1)

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Received 13 November 2012; Accepted 11 March 2013

Homologous recombination (HR) is essential for genome integrity. Recombination proteins participate in tolerating DNA lesions that interfere with DNA replication, but can also generate toxic recombination intermediates and genetic instability when they are not properly regulated. Here, we have studied the role of the recombination proteins Rad51 and Rad52 at replication forks and replicative DNA lesions. We show that Rad52 loads Rad51 onto unperturbed replication forks, where they facilitate replication of alkylated DNA by non-repair functions. The recruitment of Rad52 and Rad51 to chromatin during DNA replication is a prerequisite for the repair of the non-DSB DNA lesions, presumably single-stranded DNA gaps, which are generated during the replication of alkylated DNA. We also show that the repair of these lesions requires CDK1 and is not coupled to the fork but rather restricted to G2/M by the replicative checkpoint. We propose a new scenario for HR where Rad52 and Rad51 are recruited to the fork to promote DNA damage tolerance by distinct and cell cycle-regulated replicative and repair functions.

## **SENP3-mediated deSUMOylation of dynamin-related protein 1 promotes cell death following ischaemiaEMBO Open**

Chun Guo[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1), Keri L Hildick[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1), Jia Luo[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1), Laura Dearden[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1), Kevin A Wilkinson[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1) and Jeremy M Henley[1](http://www.nature.com/emboj/journal/vaop/ncurrent/abs/emboj201365a.html#a1)

1. School of Biochemistry, University of Bristol, University Walk, Bristol, UK

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Jeremy M Henley, School of Biochemistry, University of Bristol, University Walk, Medical Sciences Building, Bristol BS8 1TD, UK. Tel.:+44 (0)117 331 1945; Fax:+44 (0)117 331 2168; E-mail: [j.m.henley@bristol.ac.uk](mailto:j.m.henley@bristol.ac.uk)

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Global increases in small ubiquitin-like modifier (SUMO)-2/3 conjugation are a neuroprotective response to severe stress but the mechanisms and specific target proteins that determine cell survival have not been identified. Here, we demonstrate that the SUMO-2/3-specific protease SENP3 is degraded during oxygen/glucose deprivation (OGD), an *in vitro* model of ischaemia, via a pathway involving the unfolded protein response (UPR) kinase PERK and the lysosomal enzyme cathepsin B. A key target for SENP3-mediated deSUMOylation is the GTPase Drp1, which plays a major role in regulating mitochondrial fission. We show that depletion of SENP3 prolongs Drp1 SUMOylation, which suppresses Drp1-mediated cytochrome *c* release and caspase-mediated cell death. SENP3 levels recover following reoxygenation after OGD allowing deSUMOylation of Drp1, which facilitates Drp1 localization at mitochondria and promotes fragmentation and cytochrome *c* release. RNAi knockdown of SENP3 protects cells from reoxygenation-induced cell death via a mechanism that requires Drp1 SUMOylation. Thus, we identify a novel adaptive pathway to extreme cell stress in which dynamic changes in SENP3 stability and regulation of Drp1 SUMOylation are crucial determinants of cell fate

[EMBO J.](http://www.ncbi.nlm.nih.gov/pubmed/23612611) 2013 Apr 23. doi: 10.1038/emboj.2013.90. [Epub ahead of print]

**Stabilization of integrin-linked kinase by the Hsp90-CHIP axis impacts cellular force generation, migration and the fibrotic response.**

[Radovanac K](http://www.ncbi.nlm.nih.gov/pubmed?term=Radovanac%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Morgner J](http://www.ncbi.nlm.nih.gov/pubmed?term=Morgner%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Schulz JN](http://www.ncbi.nlm.nih.gov/pubmed?term=Schulz%20JN%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Blumbach K](http://www.ncbi.nlm.nih.gov/pubmed?term=Blumbach%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Patterson C](http://www.ncbi.nlm.nih.gov/pubmed?term=Patterson%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Geiger T](http://www.ncbi.nlm.nih.gov/pubmed?term=Geiger%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Mann M](http://www.ncbi.nlm.nih.gov/pubmed?term=Mann%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Krieg T](http://www.ncbi.nlm.nih.gov/pubmed?term=Krieg%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Eckes B](http://www.ncbi.nlm.nih.gov/pubmed?term=Eckes%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Fässler R](http://www.ncbi.nlm.nih.gov/pubmed?term=F%C3%A4ssler%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23612611), [Wickström SA](http://www.ncbi.nlm.nih.gov/pubmed?term=Wickstr%C3%B6m%20SA%5BAuthor%5D&cauthor=true&cauthor_uid=23612611).

**Source**

Department of Molecular Medicine, Max-Planck-Institute of Biochemistry, Martinsried, Germany.

**Abstract**

Integrin-linked kinase (ILK) is an adaptor protein required to establish and maintain the connection between integrins and the actin cytoskeleton. This linkage is essential for generating force between the extracellular matrix (ECM) and the cell during migration and matrix remodelling. The mechanisms by which ILK stability and turnover are regulated are unknown. Here we report that the E3 ligase CHIP-heat shock protein 90 (Hsp90) axis regulates ILK turnover in fibroblasts. The chaperone Hsp90 stabilizes ILK and facilitates the interaction of ILK with α-parvin. When Hsp90 activity is blocked, ILK is ubiquitinated by CHIP and degraded by the proteasome, resulting in impaired fibroblast migration and a dramatic reduction in the fibrotic response to bleomycin in mice. Together, our results uncover how Hsp90 regulates ILK stability and identify a potential therapeutic strategy to alleviate fibrotic diseases.

**EW**

[J Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/23606538) 2013 Apr 19. [Epub ahead of print]

# Pin1-FADD Interactions Regulate Fas-Mediated Apoptosis in Activated Eosinophils.

[Oh J](http://www.ncbi.nlm.nih.gov/pubmed?term=Oh%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23606538), [Malter JS](http://www.ncbi.nlm.nih.gov/pubmed?term=Malter%20JS%5BAuthor%5D&cauthor=true&cauthor_uid=23606538).

### Source

Department of Pathology, University of Texas Southwestern Medical Center, Dallas, TX 75390-9072.

### Abstract

Abnormally long-lived eosinophils (Eos) are the major inflammatory component of allergic responses in the lungs of active asthmatics. Eos recruited to the airways after allergen exposure produce and respond to IL-5 and GM-CSF, enhancing their survival. Prosurvival signaling activates Pin1, a peptidyl-prolyl cis-trans isomerase that binds to Bax and prevents its activation. How long-lived Eos, despite the continued presence of GM-CSF or IL-5, eventually undergo apoptosis to end allergic inflammation remains unclear. In this study, we show that Pin1 location, activity, and protein interactions are jointly influenced by Fas and the prosurvival cytokine IL-5. Fas signaling strongly induced the phosphorylation of FADD at Ser194 and Pin1 at Ser16, as well as their nuclear accumulation. Phospho-mimic Ser194Glu FADD mutants accelerated Eos apoptosis compared with wild-type or Ser194Ala mutants. Downstream of FADD phosphorylation, caspase 8, 9, and 3 cleavage, as well as Eos apoptosis induced by Fas, were reduced by constitutively active Pin1 and enhanced by Pin1 inhibition. Pin1 was activated by IL-5, whereas simultaneous IL-5 and anti-Fas treatment modestly reduced peptidyl isomerase activity but induced Pin1 to associate with FADDafter its phosphorylation at Ser194. Mechanistically, Pin1-mediated isomerization facilitated the subsequent dephosphorylation of Ser194 FADDand maintenance of cytoplasmic location. In vivo-activated bronchoalveolar Eos obtained after allergen challenge showed elevated survival and Pin1 activity that could be reversed by anti-Fas. Therefore, our data suggest that Pin1 is a critical link between FADD-mediated cell death and IL-5-mediated prosurvival signaling.

[J Biol Chem.](http://www.ncbi.nlm.nih.gov/pubmed/23612963) 2013 Apr 23. [Epub ahead of print]

# Diverse Sequence Determinants Control Human and Mouse Receptor Interacting Protein 3 (RIP3) and Mixed Lineage Kinase domain-Like (MLKL) Interaction in Necroptotic Signaling.

[Chen W](http://www.ncbi.nlm.nih.gov/pubmed?term=Chen%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Zhou Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhou%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Li L](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Zhong CQ](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhong%20CQ%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Zheng X](http://www.ncbi.nlm.nih.gov/pubmed?term=Zheng%20X%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Wu X](http://www.ncbi.nlm.nih.gov/pubmed?term=Wu%20X%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Zhang Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Ma H](http://www.ncbi.nlm.nih.gov/pubmed?term=Ma%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Huang D](http://www.ncbi.nlm.nih.gov/pubmed?term=Huang%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Li W](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Xia Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Xia%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23612963), [Han J](http://www.ncbi.nlm.nih.gov/pubmed?term=Han%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23612963).

### Source

Xiamen University, China;

### Abstract

RIP3 is a protein kinase essential for TNF-induced necroptosis. Phosphorylation on S227 in human RIP3 (hRIP3) is required for its interaction with hMLKL in the necrosome, a signaling complex induced by TNF stimulation. RIP1 and RIP3 mediate necrosome aggregation leading to the formation of amyloid-like signaling complexes. We found that TNF induces T231 and S232 phosphorylation in mouse RIP3 (mRIP3) and this phosphorylation is required for mRIP3 to interact with mMLKL. S232 in mRIP3 corresponds to S227 in hRIP3 while T231 is not conserved in hRIP3. Although RIP3-MLKL interaction is required for necroptosis in both human and mouse cells, hRIP3 does not interact with mMLKL and mRIP3 cannot bind to hMLKL. The species specificity of RIP3-MLKL interaction is primarily determined by the sequence differences in the phosphorylation sites and the flanking sequence around the phosphorylation sites in hRIP3 and mRIP3. It appears that RIP3-MLKL interaction has been selected as an evolutionarily conserved mechanism in mediating necroptosis signaling despite that differing structural and mechanistic bases for this interaction emerged simultaneously in different organisms. In addition, we further revealed that RIP3's interaction with MLKL prevented massive abnormal RIP3 aggregation, and therefore should be crucial for formation of the amyloid signaling complex of necrosomes. We also found that the interaction between RIP3 and MLKL is required for the translocation of necrosomes to mitochondria-associated membranes (MAM). Our data demonstrate the importance of RIP3-MLKL interaction in the formation of functional necrosomes and suggest that the translocation of necrosomes to MAM is essential for necroptosis signaling.

[Cell Biochem Funct.](http://www.ncbi.nlm.nih.gov/pubmed/23584955) 2013 Apr 15. doi: 10.1002/cbf.2972. [Epub ahead of print]

# Distinctive roles of receptor-interacting protein kinases 1 and 3 in caspase-independent cell death of L929.

[Park SY](http://www.ncbi.nlm.nih.gov/pubmed?term=Park%20SY%5BAuthor%5D&cauthor=true&cauthor_uid=23584955), [Shim JH](http://www.ncbi.nlm.nih.gov/pubmed?term=Shim%20JH%5BAuthor%5D&cauthor=true&cauthor_uid=23584955), [Cho YS](http://www.ncbi.nlm.nih.gov/pubmed?term=Cho%20YS%5BAuthor%5D&cauthor=true&cauthor_uid=23584955).

### Source

College of Pharmacy, Keimyung University, Daegu, South Korea.

### Abstract

Upon tumour necrosis factor alpha (TNFα) stimulation, cells respond actively by way of cell survival, apoptosis or programmed necrosis. The receptor-interacting proteins 1 (RIP1) and 3 (RIP3) are responsible for TNFα-mediated programmed necrosis. To delineate the differential contributions of RIP3 and RIP1 to programmed necrosis, L929 cells were stimulated with TNFα, carbobenzoxy-valyl-alanyl-aspartyl-[O-methyl]-fluoromethylketone (zVAD) or zVAD along with TNFα following RNA interference against RIP1 and RIP3, respectively. RIP1 silencing did not protect cells from TNFα-mediated cell death, while RIP3 down-regulation made them refractory to TNFα. The heat shock protein 90 inhibitor geldanamycin (GA) down-regulated both RIP1 and RIP3 expression, which rendered cells resistant to zVAD/TNFα-mediated cell death but not to TNFα-mediated cell death alone. Therefore, the protective effect of GA on zVAD/TNFα-stimulated necrosis might be attributed to RIP3, not RIP1, down-regulation. Pretreatment of L929 cells with rapamycin mitigated zVAD-mediated cell death, while the autophagy inhibitor chloroquine did not affect necrotic cell death. Meanwhile, necrotic cell death by zVAD and TNFα was caused by reactive oxygen species generation and effectively diminished by lipid-soluble butylated hydroxyanisole. Taken together, the results indicate that RIP1 and RIP3 can independently mediate death signals being transduced by two different death stimuli, zVAD and TNFα.

[Cell.](http://www.ncbi.nlm.nih.gov/pubmed/23582643) 2013 Apr 9. pii: S0092-8674(13)00344-9. doi: 10.1016/j.cell.2013.03.022. [Epub ahead of print]

# TNF Dually Mediates Resistance and Susceptibility to Mycobacteria via Mitochondrial Reactive Oxygen Species.

[Roca FJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Roca%20FJ%5BAuthor%5D&cauthor=true&cauthor_uid=23582643), [Ramakrishnan L](http://www.ncbi.nlm.nih.gov/pubmed?term=Ramakrishnan%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23582643).

### Source

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### Abstract

Tumor necrosis factor (TNF) constitutes a critical host defense against tuberculosis, but its excess is also implicated in tuberculosis pathogenesis in zebrafish and humans. Using the zebrafish, we elucidate the pathways by which TNF mediates tuberculosis pathogenesis. TNF excess induces mitochondrial reactive oxygen species (ROS) in infected macrophages through RIP1-RIP3-dependent pathways. While initially increasing macrophage microbicidal activity, ROS rapidly induce programmed necrosis (necroptosis) and release mycobacteria into the growth-permissive extracellular milieu. TNF-induced necroptosis occurs through two pathways: modulation of mitochondrial cyclophilin D, implicated in mitochondrial permeability transition pore formation, and acid sphingomyelinase-mediated ceramide production. Combined genetic blockade of cyclophilin D and acid sphingomyelinase renders the high TNF state hyperresistant by preventing macrophage necrosis while preserving increased microbicidal activity. Similarly, the cyclophilin D-inhibiting drug alisporivir and the acid sphingomyelinase-inactivating drug, desipramine, synergize to reverse susceptibility, suggesting the therapeutic potential of these orally active drugs against tuberculosis and possibly other TNF-mediated diseases.

[Immunity.](http://www.ncbi.nlm.nih.gov/pubmed/23602765) 2013 Apr 17. pii: S1074-7613(13)00146-5. doi: 10.1016/j.immuni.2013.03.008. [Epub ahead of print]

# Dimerization and Ubiquitin Mediated Recruitment of A20, a Complex Deubiquitinating Enzyme.

[Lu TT](http://www.ncbi.nlm.nih.gov/pubmed?term=Lu%20TT%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Onizawa M](http://www.ncbi.nlm.nih.gov/pubmed?term=Onizawa%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Hammer GE](http://www.ncbi.nlm.nih.gov/pubmed?term=Hammer%20GE%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Turer EE](http://www.ncbi.nlm.nih.gov/pubmed?term=Turer%20EE%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Yin Q](http://www.ncbi.nlm.nih.gov/pubmed?term=Yin%20Q%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Damko E](http://www.ncbi.nlm.nih.gov/pubmed?term=Damko%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Agelidis A](http://www.ncbi.nlm.nih.gov/pubmed?term=Agelidis%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Shifrin N](http://www.ncbi.nlm.nih.gov/pubmed?term=Shifrin%20N%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Advincula R](http://www.ncbi.nlm.nih.gov/pubmed?term=Advincula%20R%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Barrera J](http://www.ncbi.nlm.nih.gov/pubmed?term=Barrera%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Malynn BA](http://www.ncbi.nlm.nih.gov/pubmed?term=Malynn%20BA%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Wu H](http://www.ncbi.nlm.nih.gov/pubmed?term=Wu%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23602765), [Ma A](http://www.ncbi.nlm.nih.gov/pubmed?term=Ma%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23602765).

### Source

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### Abstract

A20 is an anti-inflammatory protein linked to multiple human autoimmune diseases and lymphomas. A20 possesses a deubiquitinating motif and a zinc finger, ZF4, that binds ubiquitin and supports its E3 ubiquitin ligase activity. To understand how these activities mediate A20's physiological functions, we generated two lines of gene-targeted mice, abrogating either A20's deubiquitinating activity (Tnfaip3OTU mice) or A20's ZF4 (Tnfaip3ZF4 mice). Both Tnfaip3OTU and Tnfaip3ZF4 mice exhibited increased responses to TNF and sensitivity to colitis. A20's C103 deubiquitinating motif restricted both K48- and K63-linked ubiquitination of receptor interacting protein 1 (RIP1). A20's ZF4 was required for recruiting A20 to ubiquitinated RIP1. A20OTU proteins and A20ZF4 proteins complemented each other to regulate RIP1 ubiquitination and NFκB signaling normally in compound mutant Tnfaip3OTU/ZF4 cells. This complementation involved homodimerization of A20 proteins, and we have defined an extensive dimerization interface in A20. These studies reveal how A20 proteins collaborate to restrict TNF signaling.

[Cell Death Differ.](http://www.ncbi.nlm.nih.gov/pubmed/23579241) 2013 Apr 12. doi: 10.1038/cdd.2013.28. [Epub ahead of print]

# Non-canonical kinase signaling by the death ligand TRAIL in cancer cells: discord in the death receptor family.

[Azijli K](http://www.ncbi.nlm.nih.gov/pubmed?term=Azijli%20K%5BAuthor%5D&cauthor=true&cauthor_uid=23579241), [Weyhenmeyer B](http://www.ncbi.nlm.nih.gov/pubmed?term=Weyhenmeyer%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23579241), [Peters GJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Peters%20GJ%5BAuthor%5D&cauthor=true&cauthor_uid=23579241), [de Jong S](http://www.ncbi.nlm.nih.gov/pubmed?term=de%20Jong%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23579241), [Kruyt FA](http://www.ncbi.nlm.nih.gov/pubmed?term=Kruyt%20FA%5BAuthor%5D&cauthor=true&cauthor_uid=23579241).

### Source

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### Abstract

Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL)-based therapy is currently evaluated in clinical studies as a tumor cell selective pro-apoptotic approach. However, besides activating canonical caspase-dependent apoptosis by binding to TRAIL-specific death receptors, the TRAIL ligand can activate non-canonical cell survival or proliferation pathways in resistant tumor cells through the same death receptors, which is counterproductive for therapy. Even more, recent studies indicate metastases-promoting activity of TRAIL. In this review, the remarkable dichotomy in TRAIL signaling is highlighted. An overview of the currently known mechanisms involved in non-canonical TRAIL signaling and the subsequent activation of various kinases is provided. These kinases include RIP1, IκB/ NF-κB, MAPK p38, JNK, ERK1/2, MAP3K TAK1, PKC, PI3K/Akt and Src. The functional consequences of their activation, often being stimulation of tumor cell survival and in some cases enhancement of their invasive behavior, are discussed. Interestingly, the non-canonical responses triggered by TRAIL in resistant tumor cells resemble that of TRAIL-induced signals in non-transformed cells. Better knowledge of the mechanism underlying the dichotomy in TRAIL receptor signaling may provide markers for selecting patients who will likely benefit from TRAIL-based therapy and could provide a rationalized basis for combination therapies with TRAIL death receptor-targeting drugs.Cell Death and Differentiation advance online publication, 12 April 2013;

[Cell Signal.](http://www.ncbi.nlm.nih.gov/pubmed/23612498) 2013 Apr 20. pii: S0898-6568(13)00112-5. doi: 10.1016/j.cellsig.2013.04.005. [Epub ahead of print]

# TNFR1 Signaling Kinetics: Spatiotemporal Control of Three Phases of IKK activation by Posttranslational Modification.

[Workman LM](http://www.ncbi.nlm.nih.gov/pubmed?term=Workman%20LM%5BAuthor%5D&cauthor=true&cauthor_uid=23612498), [Habelhah H](http://www.ncbi.nlm.nih.gov/pubmed?term=Habelhah%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23612498).

### Source

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### Abstract

TNFα is a pleotropic cytokine that plays a central role in the inflammatory response by activating the NF-κB signaling pathway, and is targeted in a range of chronic inflammatory diseases, underscoring the therapeutic importance of understanding its underlying molecular mechanisms. Although K63-linked ubiquitination of RIP1 by TRAF2/5 and cIAP1/2 was thought to serve as a scaffold to activate the NF-κB pathway, the recent accumulation of conflicting results has challenged the necessity of these proteins in NF-κB activation. In addition, several serine/threonine kinases have been implicated in TNFα-induced IKK activation; however, the targeted disruption of these kinases had no effect on transient IKK activation. The recent discovery of RIP1-dependent and -independent activation of the early and delayed phases of IKK and TRAF2 phosphorylation-dependent activation of the prolonged phase of IKK offers a reconciliatory model for the interpretation of contradictory results in the field. Notably, the TNFα-induced inflammatory response is not exclusively controlled by the NF-κB pathway but is subject to regulatory crosstalk between NF-κB and other context-dependent pathways. Thus further elucidation of these spatiotemporally-coordinated signaling mechanisms has the potential to provide novel molecular targets and therapeutic strategies for NF-κB intervention.

[J Immunol.](http://www.ncbi.nlm.nih.gov/pubmed/23616571) 2013 Apr 24. [Epub ahead of print]

# Galectin 1 Modulates Plasma Cell Homeostasis and Regulates the Humoral Immune Response.

[Anginot A](http://www.ncbi.nlm.nih.gov/pubmed?term=Anginot%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23616571), [Espeli M](http://www.ncbi.nlm.nih.gov/pubmed?term=Espeli%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23616571), [Chasson L](http://www.ncbi.nlm.nih.gov/pubmed?term=Chasson%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23616571), [Mancini SJ](http://www.ncbi.nlm.nih.gov/pubmed?term=Mancini%20SJ%5BAuthor%5D&cauthor=true&cauthor_uid=23616571), [Schiff C](http://www.ncbi.nlm.nih.gov/pubmed?term=Schiff%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23616571).

### Source

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### Abstract

Galectin-1 (GAL1) is an S-type lectin with multiple functions, including the control of B cell homeostasis. GAL1 expression was reported to be under the control of the plasma cell master regulator BLIMP-1. GAL1 was detected at the protein level in LPS-stimulated B cells and was shown to promote Ig secretion in vitro. However, the pattern of GAL1 expression and function of GAL1 in B cells in vivo are still unclear. In this study, we show that, among B cells, GAL1 is only expressed by differentiating plasma cells following T-dependent or T-independent immunization. Using GAL1-deficient mice we demonstrate that GAL1 expression is required for the maintenance of Ag-specific Ig titers and Ab-secreting cell numbers. Using an in vitro differentiation assay we find that GAL1-deficient plasmablasts can develop normally but die rapidly, through caspase 8 activation, under serum starvation-induced death conditions. TUNEL assays show that in vivo-generated GAL1-deficient plasma cells exhibit an increased sensitivity to apoptosis. Taken together, our data indicate that endogenous GAL1 supports plasma cell survival and participates in the regulation of the humoral immune response.

[FEBS J.](http://www.ncbi.nlm.nih.gov/pubmed/23615374) 2013 Apr 25. doi: 10.1111/febs.12303. [Epub ahead of print]

# SERPINA3K induces apoptosis in human colorectal cancer cells via activating the Fas/FasL/caspase-8signaling pathway.

[Yao Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Yao%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Li L](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Huang X](http://www.ncbi.nlm.nih.gov/pubmed?term=Huang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Gu X](http://www.ncbi.nlm.nih.gov/pubmed?term=Gu%20X%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Xu Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Xu%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Zhang Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhang%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Huang L](http://www.ncbi.nlm.nih.gov/pubmed?term=Huang%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Li S](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Dai Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Dai%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Li C](http://www.ncbi.nlm.nih.gov/pubmed?term=Li%20C%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Zhou T](http://www.ncbi.nlm.nih.gov/pubmed?term=Zhou%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Cai W](http://www.ncbi.nlm.nih.gov/pubmed?term=Cai%20W%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Yang Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Yang%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Gao G](http://www.ncbi.nlm.nih.gov/pubmed?term=Gao%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23615374), [Yang X](http://www.ncbi.nlm.nih.gov/pubmed?term=Yang%20X%5BAuthor%5D&cauthor=true&cauthor_uid=23615374).

### Source

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### Abstract

SERPINA3K, also known as kallikrein-binding protein (KBP), is a serine proteinase inhibitor with anti-inflammatory and anti-angiogenic activities. Our previous studies showed that SERPINA3K inhibited proliferation in a dose-dependent manner and induced apoptosis of endothelial cells but had no influence on SGC-7901 gastric carcinoma cells or HepG2 hepatocarcinoma cells. However, it is unknown whether SERPINA3K has a direct impact on other carcinoma cells and which mechanisms are involved. In this study, we reported for the first time that SERPINA3K not only decreased cell viability but also induced apoptosis in the colorectal carcinoma cell lines SW480 and HT-29. SERPINA3K-induced apoptosis of SW480 and HT-29 was rescued by interference with FasL shRNA. Moreover, SERPINA3K increased the expression of FasL and activatedcaspase-8. PPARγ,a transcription factor of FasL, was also up-regulated by SERPINA3K in a dose-dependent manner. The up-regulation effect of FasL induced by SERPINA3K was reversed after interference with PPARγ siRNA. These results demonstrated that SERPINA3K-induced SW480 and HT-29 cell apoptosis was mediated by the PPARγ/Fas/FasL signaling pathway. Therefore, our study provides additional insight into the direct anti-tumor function by inducing tumor cell apoptosis of SERPINA3K in colorectal tumors.

[Immunity.](http://www.ncbi.nlm.nih.gov/pubmed/23601685) 2013 Apr 18;38(4):717-28. doi: 10.1016/j.immuni.2012.12.007.

# Poly IC Triggers a Cathepsin D- and IPS-1-Dependent Pathway to Enhance Cytokine Production and Mediate Dendritic Cell Necroptosis.

[Zou J](http://www.ncbi.nlm.nih.gov/pubmed?term=Zou%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Kawai T](http://www.ncbi.nlm.nih.gov/pubmed?term=Kawai%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Tsuchida T](http://www.ncbi.nlm.nih.gov/pubmed?term=Tsuchida%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Kozaki T](http://www.ncbi.nlm.nih.gov/pubmed?term=Kozaki%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Tanaka H](http://www.ncbi.nlm.nih.gov/pubmed?term=Tanaka%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Shin KS](http://www.ncbi.nlm.nih.gov/pubmed?term=Shin%20KS%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Kumar H](http://www.ncbi.nlm.nih.gov/pubmed?term=Kumar%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23601685), [Akira S](http://www.ncbi.nlm.nih.gov/pubmed?term=Akira%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23601685).

### Source

Laboratory of Host Defense, WPI Immunology Frontier Research Center, Osaka University, Osaka 565-0871, Japan; Department of Host Defense, Research Institute for Microbial Diseases, Osaka University, Osaka 565-0871, Japan.

### Abstract

RIG-I-like receptors (RLRs) sense virus-derived RNA or polyinosinic-polycytidylic acid (poly IC) to exert antiviral immune responses. Here, we examine the mechanisms underlying the adjuvant effects of poly IC. Poly IC was taken up by dendritic cells (DCs), and it induced lysosomal destabilization, which, in turn, activated an RLR-dependent signaling pathway. Upon poly IC stimulation, cathepsin D was released into the cytoplasm from the lysosome to interact with IPS-1, an adaptor molecule for RLRs. This interaction facilitated cathepsin D cleavage of caspase 8and the activation of the transcription factor NF-κB, resulting in enhanced cytokine production. Further recruitment of the kinase RIP-1 to this complex initiated the necroptosis of a small number of DCs. HMGB1 released by dying cells enhanced IFN-β production in concert with poly IC. Collectively, these findings suggest that cathepsin D-triggered, IPS-1-dependent necroptosis is a mechanism that propagates the adjuvant efficacy of poly IC.

[Cell Death Dis.](http://www.ncbi.nlm.nih.gov/pubmed/23598415) 2013 Apr 18;4:e603. doi: 10.1038/cddis.2013.108.

# Mitotic catastrophe and cell death induced by depletion of centrosomal proteins.

[Kimura M](http://www.ncbi.nlm.nih.gov/pubmed?term=Kimura%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23598415), [Yoshioka T](http://www.ncbi.nlm.nih.gov/pubmed?term=Yoshioka%20T%5BAuthor%5D&cauthor=true&cauthor_uid=23598415), [Saio M](http://www.ncbi.nlm.nih.gov/pubmed?term=Saio%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23598415), [Banno Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Banno%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23598415), [Nagaoka H](http://www.ncbi.nlm.nih.gov/pubmed?term=Nagaoka%20H%5BAuthor%5D&cauthor=true&cauthor_uid=23598415), [Okano Y](http://www.ncbi.nlm.nih.gov/pubmed?term=Okano%20Y%5BAuthor%5D&cauthor=true&cauthor_uid=23598415).

### Source

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### Abstract

Mitotic catastrophe, which refers to cell death or its prologue triggered by aberrant mitosis, can be induced by a heterogeneous group of stimuli, including chromosome damage or perturbation of the mitotic apparatus. We investigated the mechanism of mitotic catastrophe and cell death induced by depletion of centrosomal proteins that perturbs microtubule organization. We transfected cells harboring wild-type or mutated p53 with siRNAs targeting Aurora A, ninein, TOG, TACC3, γ-tubulin, or pericentriolar material-1, and monitored the effects on cell death. Knockdown of Aurora A, ninein, TOG, and TACC3 led to cell death, regardless of p53 status. Knockdown of Aurora A, ninein, and TOG, led to aberrant spindle formation and subsequent cell death, which was accompanied by several features of apoptosis, including nuclear condensation and Annexin V binding in HeLa cells. During this process, cleavage of poly(ADP-ribose) polymerase-1, caspase-3, and caspase-9 was detected, but cleavage of caspase-8 was not. Cell death, monitored by time-lapse imaging, occurred during both interphase and M phase. In cells depleted of a centrosomal protein (Aurora A, ninein, or TOG), the rate of cell death was higher if the cells were cotransfected with siRNA against BubR1 or Mad2 than if they were transfected with siRNA against Bub1 or a control siRNA. These results suggest that metaphase arrest is necessary for the mitotic catastrophe and cell death caused by depletion of centrosomal proteins. Knockdown of centrosomal proteins led to increased phosphorylation of Chk2. Enhanced p-Chk2 localization was also observed at the centrosome in cells arrested in M phase, as well as in the nuclei of dying cells. Cotransfection of siRNAs against Chk2, in combination with depletion of a centrosomal protein, decreased the amount of cell death. Thus, Chk2 activity is indispensable for apoptosis after mitotic catastrophe induced by depletion of centrosomal proteins that perturbs microtubule organization.

***Mol Cell SJ***

**Preview**

**The Phosphatase PP2A Links Glutamine to the Tumor Suppressor p53**

[**Dana Gwinn**](javascript:void(0);)**,** [**E. Alejandro Sweet-Cordero**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00291-8)

* **Hint: Rollover Authors and Affiliations**

[Cancer Biology Program, Department of Pediatrics, Stanford University School of Medicine, Stanford, CA 94305, USA Corresponding author](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00291-8)

In this issue of *Molecular Cell*, [Reid et al., 2013](javascript:void(0);) show that glutamine withdrawal causes PP2A-mediated activation of p53 through its regulator EDD, linking levels of a critical metabolite to an important regulator of cell survival and proliferation.

**Altered Social Behavior and Neuronal Development in Mice Lacking the Uba6-Use1 Ubiquitin Transfer System**

[**Peter C.W. Lee**](javascript:void(0);)send email**,** [**Jean-Cosme Dodart**](javascript:void(0);)**,** [**Liviu Aron**](javascript:void(0);)**,** [**Lydia W. Finley**](javascript:void(0);)**,** [**Roderick T. Bronson**](javascript:void(0);)**,** [**Marcia C. Haigis**](javascript:void(0);)**,** [**Bruce A. Yankner**](javascript:void(0);)**,** [**J. Wade Harper**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00142-1)

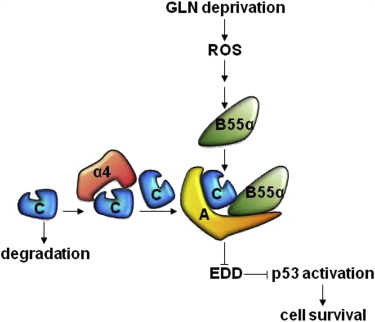
* **Hint: Rollover Authors and Affiliations**

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► Uba6 functions with Use1 as an alternative arm of the ubiquitin activation system ► Uba6 is required for neuronal morphogenesis in the hippocampus and amygdale ► Uba6 is required for proper mouse behavior ► Uba6-Use1 promotes ubiquitylation of Ube3a in vitro and Ube3a turnover in MEFs

The Uba6 (E1)-Use1 (E2) ubiquitin transfer cascade is a poorly understood alternative arm of the ubiquitin proteasome system (UPS) and is required for mouse embryonic development, independent of the canonical Uba1-E2-E3 pathway. Loss of neuronal Uba6 during embryonic development results in altered patterning of neurons in the hippocampus and the amygdala, decreased dendritic spine density, and numerous behavioral disorders. The levels of the E3 ubiquitin ligase Ube3a (E6-AP) and Shank3, both linked with dendritic spine function, are elevated in the amygdala of Uba6-deficient mice, while levels of the Ube3a substrate Arc are reduced. Uba6 and Use1 promote proteasomal turnover of Ube3a in mouse embryo fibroblasts (MEFs) and catalyze Ube3a ubiquitylation in vitro. These activities occur in parallel with an independent pathway involving Uba1-UbcH7, but in a spatially distinct manner in MEFs. These data reveal an unanticipated role for Uba6 in neuronal development, spine architecture, mouse behavior, and turnover of Ube3a.

**The B55α Subunit of PP2A Drives a p53-Dependent Metabolic Adaptation to Glutamine Deprivation**



[**Michael A. Reid**](javascript:void(0);)**,** [**Wen-I Wang**](javascript:void(0);)**,** [**Kimberly Romero Rosales**](javascript:void(0);)**,** [**Meng Xu Welliver**](javascript:void(0);)**,** [**Min Pan**](javascript:void(0);)**,** [**Mei Kong**](javascript:void(0);)send email[**See Affiliations**](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00136-6)

* **Hint: Rollover Authors and Affiliations**

[Department of Cancer Biology, Beckman Research Institute of City of Hope Cancer Center, Duarte, CA 91010, USA Department of Radiation Oncology, The Ohio State University Cancer Center, Columbus, OH 43210, USA Corresponding author](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00136-6)

► B55α is induced upon glutamine depletion and is required for tumor growth ► Glutamine deprivation-induced B55α is ROS dependent ► p53 is activated in response to low glutamine to promote cell survival ► B55α induces p53 activation through modification of a p53 regulator, EDD

Glutamine is an essential nutrient for cancer cell survival and proliferation, yet the signaling pathways that sense glutamine levels remain uncharacterized. Here, we report that the protein phosphatase 2A (PP2A)-associated protein, α4, plays a conserved role in glutamine sensing. α4 promotes assembly of an adaptive PP2A complex containing the B55α regulatory subunit via providing the catalytic subunit upon glutamine deprivation. Moreover, B55α is specifically induced upon glutamine deprivation in a ROS-dependent manner to activate p53 and promote cell survival. B55α activates p53 through direct interaction and dephosphorylation of EDD, a negative regulator of p53. Importantly, the B55α-EDD-p53 pathway is essential for cancer cell survival and tumor growth under low glutamine conditions in vitro and in vivo. This study delineates a previously unidentified signaling pathway that senses glutamine levels as well as provides important evidence that protein phosphatase complexes are actively involved in signal transduction.

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Telmo Henriques, Karen Adelman

[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00290-6) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00290-6) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513002906.pdf) (88 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00137-8) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00137-8) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001378.pdf) (1391 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00142-1) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00142-1) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001421.pdf) (2090 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00174-3) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00174-3) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001743.pdf) (2881 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00136-6) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00136-6) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513001366.pdf) (1957 kb)

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[Summary](http://www.cell.com/molecular-cell/abstract/S1097-2765(13)00205-0) | [Full Text](http://www.cell.com/molecular-cell/fulltext/S1097-2765(13)00205-0) | [PDF](http://download.cell.com/molecular-cell/pdf/PIIS1097276513002050.pdf) (2114 kb)

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**ARAM**

[Mol Cell.](http://www.ncbi.nlm.nih.gov/pubmed/23603120) 2013 Apr 16. pii: S1097-2765(13)00220-7. doi: 10.1016/j.molcel.2013.03.016. [Epub ahead of print]

**Extracellular Adenosine Sensing-A Metabolic Cell Death Priming Mechanism Downstream of p53.**

[Long JS](http://www.ncbi.nlm.nih.gov/pubmed?term=Long%20JS%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Crighton D](http://www.ncbi.nlm.nih.gov/pubmed?term=Crighton%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [O'Prey J](http://www.ncbi.nlm.nih.gov/pubmed?term=O'Prey%20J%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Mackay G](http://www.ncbi.nlm.nih.gov/pubmed?term=Mackay%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Zheng L](http://www.ncbi.nlm.nih.gov/pubmed?term=Zheng%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Palmer TM](http://www.ncbi.nlm.nih.gov/pubmed?term=Palmer%20TM%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Gottlieb E](http://www.ncbi.nlm.nih.gov/pubmed?term=Gottlieb%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23603120), [Ryan KM](http://www.ncbi.nlm.nih.gov/pubmed?term=Ryan%20KM%5BAuthor%5D&cauthor=true&cauthor_uid=23603120).

**Source**

Cancer Research UK Beatson Institute, Garscube Estate, Switchback Road, Glasgow G61 1BD, UK.

**Abstract**

Tumor cells undergo changes in metabolism to meet their energetic and anabolic needs. It is conceivable that mechanisms exist to sense these changes and link them to pathways that eradicate cells primed for cancer development. We report that the tumor suppressor p53 activates a cell death priming mechanism that senses extracellular adenosine. Adenosine, the backbone of ATP, accumulates under conditions of cellular stress or altered metabolism. We show that its receptor, A2B, is upregulated by p53. A2B expression has little effect on cell viability, but ligand engagement activates a caspase- and Puma-dependent apoptotic response involving downregulation of antiapoptotic Bcl-2 proteins. Stimulation of A2B also significantly enhances cell death mediated by p53 and upon accumulation of endogenous adenosine following chemotherapeutic drug treatment and exposure to hypoxia. Since extracellular adenosine also accumulates within many solid tumors, this distinct p53 function links programmed cell death to both a cancer- and therapy-associated metabolic change.

[J Biol Chem.](http://www.ncbi.nlm.nih.gov/pubmed/23612976) 2013 Apr 23. [Epub ahead of print]

**Downregulation of Wild-type p53-induced phosphatase 1 (Wip1) plays a critical role in regulating several p53-dependent functions in premature senescent tumor cells.**

[Crescenzi E](http://www.ncbi.nlm.nih.gov/pubmed?term=Crescenzi%20E%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Raia Z](http://www.ncbi.nlm.nih.gov/pubmed?term=Raia%20Z%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Pacifico F](http://www.ncbi.nlm.nih.gov/pubmed?term=Pacifico%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Mellone S](http://www.ncbi.nlm.nih.gov/pubmed?term=Mellone%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Moscato F](http://www.ncbi.nlm.nih.gov/pubmed?term=Moscato%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Palumbo G](http://www.ncbi.nlm.nih.gov/pubmed?term=Palumbo%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23612976), [Leonardi A](http://www.ncbi.nlm.nih.gov/pubmed?term=Leonardi%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23612976).

**Source**

Istituto di Endocrinologia e Oncologia Sperimentale, CNR, Italy;

**Abstract**

Premature or drug-induced senescence is a major cellular response to chemotherapy in solid tumors. The senescent phenotype develops slowly and is associated with chronic DNA damage response (DDR). We found that expression of Wild-type p53-induced phosphatase 1 (Wip1) is markedly downregulated during persistent DNA damage, and after drug release, during the acquisition of the senescent phenotype in carcinoma cells. We demonstrate that downregulation of Wip1 is required for maintenance of permanent G2 arrest. In fact, we show that forced expression of Wip1 in premature senescent tumor cells induces inappropriate re-initiation of mitosis, uncontrolled polyploid progression, and cell death by mitotic failure. Most of the effects of Wip1 may be attributed to its ability to dephosphorylate p53 at Ser15, and to inhibit DDR. However, we also uncover a regulatory pathway whereby suppression of p53 Ser15 phosphorylation is associated with enhanced phosphorylation at Ser46, increased p53 protein levels, and induction of Noxa expression. On the whole, our data indicate that downregulation of Wip1 expression during premature senescence plays a pivotal role in regulating several p53-dependent aspects of the senescent phenotype.

[EMBO Mol Med.](http://www.ncbi.nlm.nih.gov/pubmed/23610071) 2013 Apr 22. doi: 10.1002/emmm.201201504. [Epub ahead of print]

**Stathmin regulates mutant p53 stability and transcriptional activity in ovarian cancer.**

[Sonego M](http://www.ncbi.nlm.nih.gov/pubmed?term=Sonego%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Schiappacassi M](http://www.ncbi.nlm.nih.gov/pubmed?term=Schiappacassi%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Lovisa S](http://www.ncbi.nlm.nih.gov/pubmed?term=Lovisa%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Dall'acqua A](http://www.ncbi.nlm.nih.gov/pubmed?term=Dall'acqua%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Bagnoli M](http://www.ncbi.nlm.nih.gov/pubmed?term=Bagnoli%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Lovat F](http://www.ncbi.nlm.nih.gov/pubmed?term=Lovat%20F%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Libra M](http://www.ncbi.nlm.nih.gov/pubmed?term=Libra%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [D'Andrea S](http://www.ncbi.nlm.nih.gov/pubmed?term=D'Andrea%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Canzonieri V](http://www.ncbi.nlm.nih.gov/pubmed?term=Canzonieri%20V%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Militello L](http://www.ncbi.nlm.nih.gov/pubmed?term=Militello%20L%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Napoli M](http://www.ncbi.nlm.nih.gov/pubmed?term=Napoli%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Giorda G](http://www.ncbi.nlm.nih.gov/pubmed?term=Giorda%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Pivetta B](http://www.ncbi.nlm.nih.gov/pubmed?term=Pivetta%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Mezzanzanica D](http://www.ncbi.nlm.nih.gov/pubmed?term=Mezzanzanica%20D%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Barbareschi M](http://www.ncbi.nlm.nih.gov/pubmed?term=Barbareschi%20M%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Valeri B](http://www.ncbi.nlm.nih.gov/pubmed?term=Valeri%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Canevari S](http://www.ncbi.nlm.nih.gov/pubmed?term=Canevari%20S%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Colombatti A](http://www.ncbi.nlm.nih.gov/pubmed?term=Colombatti%20A%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Belletti B](http://www.ncbi.nlm.nih.gov/pubmed?term=Belletti%20B%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Del Sal G](http://www.ncbi.nlm.nih.gov/pubmed?term=Del%20Sal%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23610071), [Baldassarre G](http://www.ncbi.nlm.nih.gov/pubmed?term=Baldassarre%20G%5BAuthor%5D&cauthor=true&cauthor_uid=23610071).

**Source**

Division of Experimental Oncology 2, Centro di Riferimento Oncologico, National Cancer Institute, Aviano, Italy.

**Abstract**

Stathmin is a p53-target gene, frequently overexpressed in late stages of human cancer progression. Type II High Grade Epithelial Ovarian Carcinomas (HG-EOC) represents the only clear exception to this observation. Here, we show that stathmin expression is necessary for the survival of HG-EOC cells carrying a p53 mutant (p53MUT ) gene. At molecular level, stathmin favours the binding and the phosphorylation of p53MUT by DNA-PKCS , eventually modulating p53MUT stability and transcriptional activity. Inhibition of stathmin or DNA-PKCS impaired p53MUT -dependent transcription of several M phase regulators, resulting in M phase failure and EOC cell death, both in vitro and in vivo. In primary human EOC a strong correlation exists between stathmin, DNA-PKCS , p53MUT overexpression and its transcriptional targets, further strengthening the relevance of the new pathway here described. Overall our data support the hypothesis that the expression of stathmin and p53 could be useful for the identification of high risk patients that will benefit from a therapy specifically acting on mitotic cancer cells.

**SSY**

*Oncogene* advance online publication 22 April 2013; doi: 10.1038/onc.2013.115

## **STAT3 and HIF1α cooperatively activate HIF1 target genes in MDA-MB-231 and RCC4 cells**

M R Pawlus[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013115a.html#aff1), L Wang[2](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013115a.html#aff2) and C-J Hu[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013115a.html#aff1),[2](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013115a.html#aff2)

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**Abstract**

**Solid tumors often exhibit simultaneously inflammatory and hypoxic microenvironments. The ‘signal transducer and activator of transcription-3’ (STAT3)-mediated inflammatory response and the hypoxia-inducible factor (HIF)-mediated hypoxia response have been independently shown to promote tumorigenesis through the activation of HIF or STAT3 target genes and to be indicative of a poor prognosis in a variety of tumors. We report here for the first time that STAT3 is involved in the HIF1, but not HIF2-mediated hypoxic transcriptional response. We show that inhibiting STAT3 activity in MDA-MB-231 and RCC4 cells by a STAT3 inhibitor or STAT3 small interfering RNA significantly reduces the levels of HIF1, but not HIF2 target genes in spite of normal levels of hypoxia-inducible transcription factor 1α (HIF1α) and HIF2α protein. Mechanistically, STAT3 activates HIF1 target genes by binding to HIF1 target gene promoters, interacting with HIF1α protein and recruiting coactivators CREB binding protein (CBP) and p300, and RNA polymerase II (Pol II) to form enhanceosome complexes that contain HIF1α, STAT3, CBP, p300 and RNA Pol II on HIF1 target gene promoters. Functionally, the effect of STAT3 knockdown on proliferation, motility and clonogenic survival of tumor cells *in vitro* is phenocopied by HIF1α knockdown in hypoxic cells, whereas STAT3 knockdown in normoxic cells also reduces cell proliferation, motility and clonogenic survival. This indicates that STAT3 works with HIF1 to activate HIF1 target genes and to drive HIF1-depedent tumorigenesis under hypoxic conditions, but also has HIF-independent activity in normoxic and hypoxic cells. Identifying the role of STAT3 in the hypoxia response provides further data supporting the effectiveness of STAT3 inhibitors in solid tumor treatment owing to their usefulness in inhibiting both the STAT3 and HIF1 pro-tumorigenic signaling pathways in some cancer types.**

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## **Inactivation of TGF-β signaling and loss of *PTEN* cooperate to induce colon cancer *in vivo***

M Yu[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff1), P Trobridge[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff1), Y Wang[2](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff2),[3](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff3), S Kanngurn[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff1),[4](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff4), S M Morris[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff1), S Knoblaugh[5](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff5) and W M Grady[1](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff1),[3](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html#aff3)

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**Abstract**

**The accumulation of genetic and epigenetic alterations mediates colorectal cancer (CRC) formation by deregulating key signaling pathways in cancer cells. In CRC, one of the most commonly inactivated signaling pathways is the transforming growth factor-beta (TGF-β) signaling pathway, which is often inactivated by mutations of *TGF-β type II receptor* (*TGFBR2*). Another commonly deregulated pathway in CRC is the phosphoinositide-3-kinase (PI3K)-AKT pathway. Phosphatase and tensin homolog deleted on chromosome 10 (*PTEN*) is an important negative regulator of PI3K-AKT signaling and is silenced in ~30% of CRC. The combination of *TGFBR2* inactivation and loss of *PTEN* is particularly common in microsatellite-unstable CRCs. Consequently, we determined *in vivo* if deregulation of these two pathways cooperates to affect CRC formation by analyzing tumors arising in mice that lack *Tgfbr2* and/or *Pten* specifically in the intestinal epithelium. We found that lack of *Tgfbr2 (Tgfbr2IEKO*) alone is not sufficient for intestinal tumor formation and lack of *Pten* (*PtenIEKO*) alone had a weak effect on intestinal tumor induction. However, the combination of *Tgfbr2* inactivation with *Pten* loss (*PtenIEKO;Tgfbr2IEKO*) led to malignant tumors in both the small intestine and colon in 86% of the mice and to metastases in 8% of the tumor-bearing mice. Moreover, these tumors arose via a β-catenin-independent mechanism. Inactivation of TGF-β signaling and loss of *Pten* in the tumors led to increased cell proliferation, decreased apoptosis and decreased expression of cyclin-dependent kinase inhibitors. Thus, inactivation of TGF-β signaling and loss of *PTEN* cooperate to drive intestinal cancer formation and progression by suppressing cell cycle inhibitors.**

**Reviews**

**Tumor stroma: a complexity dictated by the hypoxic tumor microenvironment**

A Casazza, G Di Conza, M Wenes, V Finisguerra, S Deschoemaeker and M Mazzone

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.121

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013121a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013121a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013121a.pdf)

**Sorting out functions of sirtuins in cancer**

M Roth and W Y Chen

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.120

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013120a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013120a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013120a.pdf)

**Multilayer control of the EMT master regulators**

H Zheng and Y Kang

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.128

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**Original Articles**

**Malignant melanoma cells acquire resistance to DNA interstrand cross-linking chemotherapeutics by p53-triggered upregulation of DDB2/XPC-mediated DNA repair**

C Barckhausen, W P Roos, S C Naumann and B Kaina

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.141

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**Cadherin-17 interacts with α2β1 integrin to regulate cell proliferation and adhesion in colorectal cancer cells causing liver metastasis**

R A Bartolomé, R Barderas, S Torres, M J Fernandez-Aceñero, M Mendes, J García-Foncillas, M Lopez-Lucendo and J I Casal

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.117

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013117a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013117a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013117a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013117s1.html)

**Loss of TSC2 confers resistance to ceramide and nutrient deprivation**

G G Guenther, G Liu, M U Ramirez, R J McMonigle, S M Kim, A N McCracken, Y Joo, I Ushach, N L Nguyen and A L Edinger

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[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013139a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013139a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013139a.pdf)

**Protein kinase Cα suppresses *Kras*-mediated lung tumor formation through activation of a p38 MAPK-TGFβ signaling axis**

K S Hill, E Erdogan, A Khoor, M P Walsh, M Leitges, N R Murray and A P Fields

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.147

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013147a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013147a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013147a.pdf)

**RRP1B is a metastasis modifier that regulates the expression of alternative mRNA isoforms through interactions with SRSF1**

M Lee, A M Dworkin, D Gildea, N S Trivedi, NISC Comparative Sequencing Program, G B Moorhead and N P S Crawford

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[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013133a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013133a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013133a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013133s1.html)

**Targeting homologous recombination and telomerase in Barrett’s adenocarcinoma: impact on telomere maintenance, genomic instability and tumor growth**

R Lu, J Pal, L Buon, P Nanjappa, J Shi, M Fulciniti, Y-T Tai, L Guo, M Yu, S Gryaznov, N C Munshi and M A Shammas

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.103

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**ING4 regulates a secretory phenotype in primary fibroblasts with dual effects on cell proliferation and tumor growth**

A Moreno, I Soleto, P García-Sanz, G Moreno-Bueno and I Palmero

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.145

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013145a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013145a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013145a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013145s1.html)

**STAT3 and HIF1α cooperatively activate HIF1 target genes in MDA-MB-231 and RCC4 cells**

M R Pawlus, L Wang and C-J Hu

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.115

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**HBx-mediated miR-21 upregulation represses tumor-suppressor function of PDCD4 in hepatocellular carcinoma**

X Qiu, S Dong, F Qiao, S Lu, Y Song, Y Lao, Y Li, T Zeng, J Hu, L Zhang, L Zhang and H Fan

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.150

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013150a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013150a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013150a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013150s1.html)

**Activation of mitogen- and stress-activated kinase 1 is required for proliferation of breast cancer cells in response to estrogens or progestins**

D Reyes, C Ballaré, G Castellano, D Soronellas, J R Bagó, J Blanco and M Beato

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.95

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc201395a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc201395a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc201395a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc201395s1.html)

**The role of DAB2IP in androgen receptor activation during prostate cancer progression**

K Wu, J Liu, S-F Tseng, C Gore, Z Ning, N Sharifi, L Fazli, M Gleave, P Kapur, G Xiao, X Sun, O K Oz, W Min, G Alexandrakis, C-R Yang, C-L Hsieh, H-C Wu, D He, D Xie and J-T Hsieh

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[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013143a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013143a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013143a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013143s1.html)

**ACP5, a direct transcriptional target of FoxM1, promotes tumor metastasis and indicates poor prognosis in hepatocellular carcinoma**

L Xia, W Huang, D Tian, Z Chen, L Zhang, Y Li, H Hu, J Liu, Z Chen, G Tang, J Dou, S Sha, B Xu, C Liu, J Ma, S Zhang, M Li, D Fan, Y Nie and K Wu

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.90

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc201390a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc201390a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc201390a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc201390s1.html)

**Inactivation of TGF-β signaling and loss of *PTEN* cooperate to induce colon cancer *in vivo***

M Yu, P Trobridge, Y Wang, S Kanngurn, S M Morris, S Knoblaugh and W M Grady

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.102

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013102a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013102a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013102a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013102s1.html)

**Synergy between Kaposi's sarcoma-associated herpesvirus (KSHV) vIL-6 and HIV-1 Nef protein in promotion of angiogenesis and oncogenesis: role of the AKT signaling pathway**

X Zhu, Y Guo, S Yao, Q Yan, M Xue, T Hao, F Zhou, J Zhu, D Qin and C Lu

Oncogene advance online publication, April 22, 2013; doi:10.1038/onc.2013.136

[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013136a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013136a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013136a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013136s1.html)

**Short Communication**

**MYC, a downstream target of BRD-NUT, is necessary and sufficient for the blockade of differentiation in NUT midline carcinoma**

A R Grayson, E M Walsh, M J Cameron, J Godec, T Ashworth, J M Ambrose, A B Aserlind, H Wang, G I Evan, M J Kluk, J E Bradner, J C Aster and C A French

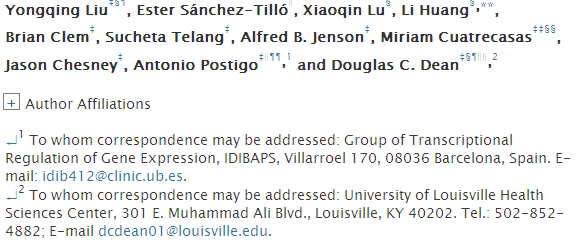
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[Abstract](http://www.nature.com/onc/journal/vaop/ncurrent/abs/onc2013126a.html) | [Full Text](http://www.nature.com/onc/journal/vaop/ncurrent/full/onc2013126a.html) | [PDF](http://www.nature.com/onc/journal/vaop/ncurrent/pdf/onc2013126a.pdf) | [Supplementary information](http://www.nature.com/onc/journal/vaop/ncurrent/suppinfo/onc2013126s1.html)

**MH**

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**Sequential Inductions of the ZEB1 Transcription Factor Caused by Mutation of Rb and Then Ras Proteins Are Required for Tumor Initiation and Progression**[**\***](http://www.jbc.org/content/288/16/11572.abstract#fn-1)



**Capsule**

**Background:** Ras mutation drives tumor initiation as well as invasion.

**Results:** The ZEB1 transcription factor is sequentially induced with mutation of Rb1 and Ras, and these inductions are required for Ras-mediated tumor initiation and then invasion.

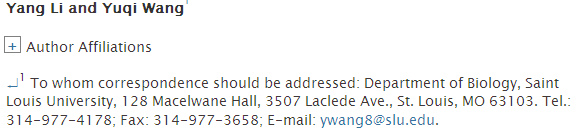
**Conclusion:** ZEB1 plays a critical role in initiation and progression of Ras-mediated tumors.

**Significance:** Induction ZEB1 is important for tumor initiation and invasion in a model of Ras-initiated cancer.

**Abstract**

Rb1 restricts cell cycle progression, and it imposes cell contact inhibition to suppress tumor outgrowth. It also triggers oncogene-induced senescence to block Ras mutation. Loss of the Rb1 pathway, which is a hallmark of cancer cells, then provides a permissive environment for Ras mutation, and Ras is sufficient for invasive tumor formation in Rb1 family mutant mouse embryo fibroblasts (MEFs). These results demonstrate that sequential mutation of the Rb1 and Ras pathways comprises a tumor initiation axis. Both Rb1 and Ras regulate expression of the transcription factor ZEB1, thereby linking tumor initiation to the subsequent invasion and metastasis, which is induced by ZEB1. ZEB1 acts in a negative feedback loop to block expression of miR-200, which is thought to facilitate tumor invasion and metastasis. However, ZEB1 also represses cyclin-dependent kinase (cdk) inhibitors to control the cell cycle; its mutation in MEFs leads to induction of these inhibitors and premature senescence. Here, we provide evidence for two sequential inductions of ZEB1 during Ras transformation of MEFs. Rb1 constitutively represses cdk inhibitors, and induction of ZEB1 when the Rb1 pathway is lost is required to maintain this repression, allowing for the classic immortalization and loss of cell contact inhibition seen when the Rb1 pathway is lost. In vivo, we show that this induction of ZEB1 is required for Ras-initiated tumor formation. ZEB1 is then further induced by Ras, beyond the level seen with Rb1 mutation, and this Ras superinduction is required to reach a threshold of ZEB1 sufficient for repression of miR-200 and tumor invasion.

**Ras Protein/cAMP-dependent Protein Kinase Signaling Is Negatively Regulated by a Deubiquitinating Enzyme, Ubp3, in Yeast**

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**Capsule**

**Background:** Ras proteins are important molecular switches. RasGAP is an essential negative regulator of Ras, and its activity is controlled by ubiquitination.

**Results:** RasGAP interacts with a deubiquitinating enzyme, Ubp3. Disrupting Ubp3 activity leads to accumulation of ubiquitinated RasGAP and hyperactivation of Ras signaling.

**Conclusion:** Appropriate deubiquitination of RasGAP by Ubp3 is important for Ras signaling.

**Significance:** This study reveals a new layer of mechanism that regulates Ras.

**Abstract**

Ras proteins and cAMP-dependent protein kinase (protein kinase A, PKA) are important components of a nutrient signaling pathway that mediates cellular responses to glucose in yeast. The molecular mechanisms that regulate Ras/PKA-mediated signaling remain to be fully understood. Here, we provide evidence that Ras/PKA signaling is negatively regulated by a deubiquitinating enzyme, Ubp3. Disrupting the activity of Ubp3 leads to hyperactivation of PKA, as evidenced by much enhanced phosphorylation of PKA substrates, decreased accumulation of glycogen, larger cell size, and increased sensitivity to heat shock. Levels of intracellular cAMP and the active forms of Ras proteins are also elevated in the *ubp3*Δ mutant. Consistent with a possibility that the increased cAMP is responsible for the abnormal signaling behavior of the *ubp3*Δ mutant, overexpressing *PDE2*, which encodes a phosphodiesterase that hydrolyzes cAMP, significantly relieves the cell size increase and heat shock sensitivity of the mutant. Further analysis reveals that Ubp3 interacts with a Ras GTPase-accelerating protein, Ira2, and regulates its level of ubiquitination. Together, our data indicate that Ubp3 is a new regulator of the Ras/PKA signaling pathway and suggest that Ubp3 regulates this pathway by controlling the ubiquitination of Ras GTPase-accelerating protein Ira2.